Denver Metro Emergency Medical Services (EMS) Medical Directors
Statement for Prehospital Providers Regarding the
Update to 6010 Agitated/Combative Patient Protocol

Shared Goal: To create a framework for emergency medical care within our community that supports safe and effective treatment and transport of patients experiencing medical emergencies to the hospital built on the most up to date and patient-safety centered medical literature.

Why are we making changes to the sedation protocol?

The Denver Metro EMS Medical Directors are updating the sedation protocol to reflect evidence-based practice in prehospital medicine. Our intention in this update is to ensure a patient-centered policy that minimizes risks to the patient and to individuals providing emergency care while supporting paramedics in their individual clinical practices. The changes made here have been shown through multiple clinical trials to reduce the risk of adverse events.

Please be aware that these updates are agreed upon by the Denver Metro EMS Medical Directors, physician experts who reviewed and collectively developed this as regional best practice. While each agency has the ability and responsibility to adapt these to the needs of the patients that they serve, this is our regional recommendation.

What are the changes being made?

- There is now an initial dose of **up to** 5 mg of intravenous midazolam or equivalent dose of alternative benzodiazepines.
    - This comes with the recommendation to give a lower dose of benzodiazepines when clinically appropriate.
- After administering the first dose of benzodiazepine, switch to a butyrophenone or contact base for additional benzodiazepine dosing.
- The selection of the ***first*** agent used for the sedation of the agitated patient is left to the discretion of the paramedic to allow prehospital providers to use their clinical judgement depending on the suspected etiology of the severely agitated behavior.
- Once two administrations of ***any*** sedating agent are given, regardless of agents or doses administered, any further medication doses will require a base order.

Why use a combination of two medications instead of additional doses of a single agent?

Current medical literature suggests that a two-medication combination of different mechanisms of action is superior to a single agent when attempting to sedate a patient with acute agitation. Chan et al (2013) studied midazolam alone versus combining droperidol

(Inapsine) and midazolam (Versed) or olanzapine (Zyprexa) and midazolam. This included reducing the midazolam dose for patients weighing less than 50 kg (2.5 mg for patients < 50 kg, 5.0 mg for patients ≥ 50 kg). Their result was a decreased time to sedation with the combination of medications, but no difference in the rate of adverse effects or emergency department length of stay. Taylor et al (2016) produced a similar study, comparing the effects of midazolam and droperidol (5 mg of each) versus 10 mg of either droperidol or olanzapine. The results of this study showed that sedation was achieved at both five and ten minutes in a greater percentage of patients using the dual medication approach than either single agent approach. Furthermore, there was no difference in adverse events, and there was a lower need for additional redosing of sedating medications in the combination therapy group. While the two previous studies looked at all patients with agitation, Yap et al (2017) looked specifically at the sedation of patients under the influence of methamphetamines. In this study, they compared the same combination as Taylor et al (2016), with 85% of patients achieving sedation with the combination therapy at ten minutes compared to 47% in the droperidol group and 50% in the olanzapine group.

While the previously mentioned studies demonstrated no difference in adverse events between the different sedation protocols, other studies did show a significant difference. Knott et al (2006) compared midazolam and droperidol as single agents for sedation. In this study, the midazolam group had a significant increase in the need for active away management relative to the droperidol group, with the risk being increased as the dose required to achieve sedation was increased. Isbister et al (2010) compared intramuscular administration (10 mg of droperidol, 10 mg of midazolam, or 5 mg of each in combination). In this trial, there was no difference in the time to sedation, but the combination therapy resulted in a few adverse events, most of which were related to a decrease in oxygen saturation or airway obstruction. Moreover, the droperidol-only group had no significant increase in the patient's QTc.

While most of these studies took place in the emergency department, we feel that they represent the patients that our prehospital providers encounter. Therefore, we believe that the combination therapy described in these studies and introduced into these protocols represents the safest and most efficacious care for the community we serve.

In which patients should a *reduced* initial dose of midazolam be considered?

Midazolam is a benzodiazepine that works by increasing the frequency of the GABA channels opening in the central nervous system, thus causing an inhibitory effect and resulting in sedation. Although no two patients are identical, and therefore the potential effects of a medication cannot be entirely predicted, there are some circumstances during which a lower initial dose is indicated.

Given that midazolam and alcohol both act as GABA receptor agonists, there is an increased potential for significant sedation and resultant respiratory depression with this combination.

This is also extended to other benzodiazepines, such as diazepam and alprazolam. While opiates and opioids act through a different mechanism than benzodiazepines, the combination of the two can result in significant respiratory depression, and a reduced dose should be considered. This should be extended to other sedating agents, including barbiturates, tricyclic antidepressants, and any other sedating medications or sedating substances.

There are also several attributes of the metabolism of benzodiazepines that should be considered when determining the appropriate dose. The resultant effect of a medication is based on the serum concentration of the medication. In other words, patients with a lower weight will experience a greater sedating effect from the same dose compared to a larger patient and thus should receive a smaller initial dose. Furthermore, benzodiazepines are lipophilic and thus are readily absorbed into the tissues of the body. Therefore, patients with lower BMIs will likely experience a greater sedating effect than those with same weight but a higher BMI. For those with hepatic impairment (liver disease, using medications that affect liver function such as statins), the metabolism of benzodiazepines is slowed, resulting in greater blood concentrations and resultant sedation (Nordt et al, 1997). There is a similar effect from renal impairment, as the drug cannot be eliminated as quickly, resulting in increased concentrations and effect.

In addition to weight, the age of the patient must also be considered when selecting an appropriate sedative dose. Older adults (>65 years old) are more likely to have increased sedation and resulting adverse events or paradoxical reactions to benzodiazepines. Additionally, they are often at higher risk for adverse events with the administration of benzodiazepines given their comorbidities. For these reasons, we recommend using a lower dose initially in older adults, as well as considering and treating organic causes of agitation.

Bibliography

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