Benzodiazepines

Benzodiazepines are the most commonly used medications for oral sedation mainly because of their wide margin of safety. The main effects of benzodiazepines are anxiolysis (calming effect), sedation, amnesia and muscle relaxation. At very high doses, and in combination with other medications, respiratory depression and cardiac depression are possible.

All benzodiazepines and the so called non-benzodiazepine-GABA agonists (Lunesta, Ambien) work by binding to the benzodiazepine receptor on the GABA complex. When the benzodiazepine receptor is activated it modulates GABA (the main inhibitory neurotransmitter in the brain) to bind more readily to the GABA receptor, which causes chloride channels to open (the main inhibitory effect). An important point regarding this mechanism of action is that benzodiazepines only act indirectly with GABA, they can't independently open chloride channels without GABA (unlike chloral hydrate, barbiturates, or propofol). This accounts for why benzodiazepines have somewhat of a ceiling effect and a large margin of safety.

All benzodiazepines will cause similar effects in a dose dependent manner. One should chose the agent based on the needed duration of action. Triazolam (Halcion) and diazepam (Valium) are relatively short acting benzodiazepines, while lorazepam (Ativan) and alprazolam (Xanax) are longer acting benzodiazepines. Despite its long elimination half life, Valium is a short acting medication because it has a short distribution half life (1-3 hours based off its degree of lipid solubility and how quickly it enters and leaves the brain).

Non-Benzodiazepine-GABA agonists

More recently drug companies have marketed drugs that are non benzodiazepines in how they are chemically synthesized, but are agonist on the benzodiazepine receptors. Thus, despite marketing claims, they act clinically like benzodiazepines and can also be reversed by flumazenil just like other benzodiazepines. These drugs include zolpidem (Ambien), zaleplon (Sonata) and eszopiclone (Lunesta). For example, 10mg Ambien would be nearly identical to 0.25mg Halcion except that Ambien is more expensive.
**Antihistamines**

Antihistamines main use is in prevention of allergies/allergic reactions due to histamine release from mast cell degranulation by blocking the H1 histamine receptor. These medications also have anticholinergic effects which can cause dry mouth as well as antiemetic and mildly antitussive (inhibit cough).

First generation antihistamines all cross the blood-brain barrier and thus cause drowsiness and sedation. Second generation antihistamines, like loratadine (Claritin), don’t readily cross the blood-brain barrier and don’t cause nearly as much drowsiness. Common first generation antihistamines used in oral sedation are diphenhydramine (benadryl), hydroxyzine (Atarax, Vistaril) and promethazine (Phenergan). Hydroxyzine has been reported to have anxiolytic properties as well as sedative properties. As a group, the antihistamines are not as effective of a sedative hypnotic as the benzodiazepines. They have a very wide margin of safety, because when used alone, at normal dose ranges, they cause no respiratory/cardiac depression. These agents are sometimes used in a cocktail approach.

**Opioids**

Opioids are not generally used for oral sedation as they have little anxiolytic properties, and can cause more respiratory depression. However, some have added meperidine (Demerol) into cocktails for oral sedation (chloral hydrate, Vistaril, Demerol). As discussed later, drug synergism with oral medications can lead to a more varied response with specific individuals than with a one drug approach. When used with other sedative hypnotics the effect of opioids is synergistically increased.

**Miscellaneous Agents: Chloral Hydrate and Ketamine**

Chloral hydrate (Noctec) was one of the first sedative hypnotic agents available, being synthesized in 1832. It was used commonly in pediatric sedation with a cocktail of other medications. It worked as a general CNS depressant and was able to induce deep sedation within 30 minutes. As other agents, such as oral midazolam (Versed), have become more standard in pediatric oral sedation, the use of chloral hydrate has diminished. Recently, manufactures have stopped producing the drug.

Ketamine is a NMDA antagonist which causes a dissociative anesthesia, basically by “disconnecting” the cerebral cortex from the thalamus/limbic system, thus the patient is dissociated from any pain or fear that they may be feeling. This medication has many unique properties from the other sedative hypnotics including: analgesia, hallucinations, hyper-salivation, emetogenic, and a cardiac stimulatory effect. Ketamine tends to maintain airway reflexes and has very little effect on respiratory function. Since Ketamine is a general anesthetic, the Oregon dental board states that only those with a general anesthesia permit can use ketamine.

**Multiple Drug Synergism**

One key point with oral sedation is the fact that each drug has a dose response curve and as the dose increases the level of sedation and possible side effects also increase. There are always those who are hyper and hypo responders. Oral sedation effects are somewhat unpredictable because the dose cannot be titrated to effect like with IV medications. This becomes even more important when multiple medications are given in combination. For example, meperidine, chloral hydrate, and hydroxyzine have been used in the past for pediatric oral sedation. This cocktail allowed for drug synergism such that the combination of drugs could produce a markedly greater effect than the sum of the individual drugs and a patient could become more sedated than the intended level. This means that the dose needed to reach unconsciousness became much lower if used in combination with other medications than if used alone (Vinik 1994), thus making over sedation more likely to occur, such as in the recent Hawaii oral sedation death which used this combination.
Dr. Ryan Allred is a dentist anesthesiologist practicing in the Portland, Oregon area. He travels to dental offices providing all levels of anesthesia, from IV sedation to general anesthesia, for pediatric, adult and medically complex patients. This allows both dentist and patient to have a smooth and comfortable experience in some of the most challenging cases. More information about Dr. Allred’s training and services offered by Portland Dental Anesthesia can be found at www.portlanddentalanesthesia.com.

If you would like meet with Dr. Allred or if you would like help integrating the new CO\textsubscript{2} (capnography) rules in your office, call 503-858-4880.

If you have a patient in your office that might need deep sedation or general anesthesia, please call 503-858-4880.
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