Anesthesia in odontoiatria

GUIDELINES ON THE USE OF LORAZEPAM FOR ENTERAL CONSCIOUS SEDATION

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Sedation in dentistry* is continuously under review and study in order to achieve the maximum safety during the procedure. The use of conscious sedation in dentistry** is related to the anxiety associated with experiencing pain during the dental treatment. Conscious sedation provides a depression of the central nervous system (CNS) during which verbal communication is not altered all along the procedure. At the same time airways remain clear.[1] Dental practitioners' preferred technique is intravenous (IV) sedation in the 80% of the cases, and enteral sedation in the 30% of the dentists.[2,3] The preferences are related to titration being more difficult during enteral procedure[4], post-graduated training required for the use of single or multiple medications technique[5] and complex pharmacokinetics of the drugs involved in the procedure. Benzodiazepines are the most common drugs used in Europe for conscious sedation and their use varies between the different countries.[6,7] The dentist must be able to choose the most appropriate drug depending on their characteristics: site of action[8], if they are tranquillizers, hypnotic medications[9], what is their pharmacokinetics and pharmacodynamics.[10.11]

Clinical effects and site of action of benzodiazepines. Benzodiazepines have effects on different part of the body. Action sites are distributed on the grey matter, mostly in the anterior part of the brain. Secondarily, depending on the type of benzodiazepine used, heart, platelets, adrenal system and other part of the brain such as midbrain, hypothalamus and hippocampus and bone marrow are involved too. Benzodiazepines like diazepam, which has got long elimination half-life, but also benzodiazepines with short or medium half-life, act on the lateral part of the amygdala as allosteric modulators of the $GABA_A$ receptors.[12] Benzodiazepines can be also found in the synapses of descendent bundles modulating the pain on the spinal marrow.[13] Enteral conscious sedation***should prioritize drugs which are more specific for $GABA_A$-α_2 receptors connected with anxiety and muscle relaxation. For this reason, medications more compatible with $GABA_A$-α_1 receptors should be avoided as they cause sedation, anti-convulsive reactions and amnesia.[14] As those

medications act on the central nervous system, not all the effects can be predicted. Dental practitioners should be able to choose the medications that can control anxiety levels.[15] Drugs should be also chosen depending on the regulations of the country they belong to.[16]

Sedation induction through co-enteral sedation. In enteral sedation is important to know how to associate different benzodiazepines with tranquillizer features. Usually, two drugs are enough to reach a positive outcome. Particularly in IV sedation, drugs with tranquillizer properties should be preferred and titration should be performed to avoid exceeding the dosage. Co-induction technique****, which is common in Intensive Care, can be applied to IV sedation. The method consists in combining different drugs which are similar or different between them, with morphine type medications and sleep medications. That method[17] allows to reduce the length of the operative time and the costs, provides more safety and is easier to control. Co-induction technique****, if applied in enteral sedation in dentistry, requires the dental practitioner to know the pharmacokinetics, pharmacodynamics and the effects of the drugs used.[18]
Co-enteral sedation****** can be applied once a safe method has been identified and the appropriate drugs have been chosen. It must be set up on a maximum safety principle and respecting the principles[19] of conscious sedation following which no need to manage upper airways and cardiac system is needed in conscious sedation.[20] Benzodiazepines should be chosen based on the rapidity of the effect, low length of action time, fast clearance and no active metabolites produced (table 1).
In co-enteral sedation******, medications used for sleep induction or anxiety are more appropriate than benzodiazepines with low tranquillizer effects. In this study the benzodiazepine used is lorazepam, associated with chlordemethyldiazepam (CDDZ) if needed.

Co-conscious enteral Sedation principles. Phases: The method of co-conscious enteral sedation in dentistry presents the following phases:

- Sleep induction the night before the treatment with enteral lorazepam 2mg at 8.00 pm (fig.1);
- Treatment performed in the morning;
- Tranquillizer induction in surgery with enteral lorazepam 1mg (fig.2);
- Second dosage of lorazepam 1mg 60 minutes before the procedure, even in the journey to the dental practice;
- Second dosage allows a Co-enteral conscious sedation***** as a result of the residual elimination of the first dose and the absorption of the second one;
- Patient enters the surgery after 60 minutes of second dose and evaluation of the tranquillizer effect with Visual Analogue Scale (VAS);
- End point of relaxation should be measured in points;
- When end point is satisfactory for the patient (VAS = 10 points) the dentist can perform the treatment without any further dose;
- If VAS not maximal, enteral CDDZ can be given;
- In this case treatment will be delayed approximately 5-7 minutes after CDDZ dose;
- CDDZ dose is calculated on the VAS level (fig.3);
- CDDZ dose is taken with syringe 1ml;
- Conversion dose from ml to mg is 1ml of CDDZ = 1mg of CDDZ;
- CDDZ doses are calculated on the basis of the fraction as explained in fig.3.

Table 1. Strong action benzodiazepines. CDDZ is a low action benzodiazepine with long t½β half-life elimination and immediate effect.

Drugs (**strong action**)	dose (mg)	Initial effect (min)	t½β (hours)	time before pick (hours)	active metabolites (yes/NO)
Alprazolam	0,50 – 0.75	60 - 90	6 - 12	2	NO
Lorazepam	1	30 - 60	10 - 20	1,5 - 2,0	NO
Triazolam	1	30	2 - 4	1	NO
Clonazepam	0,5	60	40	4	NO
Brotizolam	0,5	8	5	1	NO
Drugs **(low action**)					
CDDZ	1-2	4 - 2	115	1 – 2	lorazepam

Drugs. Drugs used in co-enteral conscious sedation***** must belong to the benzodiazepine group with strong tranquillizer effect (table 1). Their properties are: [21]

- Low interval between assumption and tranquillizer effect;
- Short or medium t½β;
- Maximum plasmatic concentration time is short. That allows to give more than one dose during the day at regular intervals for anxiety treatment;
- They require lower dosage compared to low effect benzodiazepines;
- They can bind receptors $GABA_A$, specifically they bind receptors with sub-units $GABA_A$-α_1-α_2-α_3 and -α_5 together with sub-units -β and -ϒ.[22] The pharmacokinetics of strong effect benzodiazepines tells us that those medications have a selective action on sub-units $GABA_A$-α_2 producing tranquillizer effects. Other benzodiazepines are more selective for sub-units $GABA_A$--- -α_1[23] producing mainly sedation effects. In table 2 are indicated the sub-units $GABA_A$ -ergic related to each different effect.

Table 2. Illustration of the effects of each different sub-units contained in receptors $GABA_A$. Selective effect of strong Benzodiazepines for receptors -α_2 results in a tranquillizer effect. $GABA_A$-α_2, sub-unity is the most important mediator in the physiopathology of the anxiety disorders.

Sub-unit	α_1	α_2	α_3	α_5
Sedation	+	-	-	-
Amnesia anterograde	+	ND	ND	ND
Anti-convulsion	+	-	-	-
Tranquillizer	-	+	-	-
Muscle-resolution	-	+	+	+

ND = no determinate

Treatment in co-enteral conscious sedation. Pre-operative assessment of the patient needs to be done following this scheme: [24]

- Dentist needs to estimate the type of the treatment, medical history, interactions between the medications that the patient is on and the benzodiazepines, obtained informed consent and speak to the patient's GP if needed;
- Pre-op assessment few days before the treatment;
- Patient needs to be escorted to the practice and back home from the same person;
- The chaperone is responsible of administering the first dose of lorazepam the night before the procedure;
- The chaperone is responsible of conserving and administering the second dose of lorazepam before the treatment;
- The chaperone needs to be aware and to understand the effect of the sedation treatment;
- Chaperone and patient need to check the doses given the night before and the day of the treatment before going to the dental surgery;
- Drugs need to be kept in a safe container belonging to the dentist; the container will be given back to him at the chek-in;
- Responsible of the container is the chaperone;
- The container's content is one 2mg tablet of lorazepam, which will be taken the night before the procedure and 1 mg tablet of lorazepam administered 1 hour before the treatment;
- Patient will be given dietary post-op instructions. No alcohol assumption the day before the procedure.
- Patient parameters will be monitored during the treatment and at home from his/her chaperone;
- Patient and chaperone will be informed about Benzodiazepines effects.

Complications. In pregnancy lorazepam can interfere with fetus health. Patients who have had alcohol before the procedure may experience over-dosage symptoms and drowsiness. Contraindications are glaucoma, allergy to benzodiazepines, COPD, kidney disease, liver disease and myasthenia gravis. Patients with Major depression may become suicidal.

Conclusions. Co-enteral conscious sedation***** can be performed if compatible with the length of the dental treatment and the type of Benzodiazepine used. The dental practitioner should use doses which do not exceed in a loss of consciousness. Lorazepam's pick of action is 60-90 minutes after administering the drug (table 1). Pick's concentration remains constant for 120-180 minutes and the length is compatible with oral surgical procedures.[25,26] If additional doses are added the enteral sedation level will become from moderate to deep.[27] Deeper levels of sedation are not compatible with dental guidelines in Europe. This kind of procedure would require the dentist to be confident with general anesthetic protocols too (facial mask, ventilation, anesthetic gas, intubation).[28]

To produce an enteral sedation, the minimum effective dose is required (MED).[29] For triazolam this dose is 0,25mg. Using the maximum dose required (MRD) which is 0,5mg the patient can lose consciousness. The same effect can also occur with fractioned doses up to 0,50-0,75mg which produce moderate or deep sedation.[30] Sublingual triazolam can give higher concentration, stronger tranquillizer effect [31] compared to the enteral administration[32] and more bioavailability (28%). The hypnotic and tranquillizer effect of triazolam bind the receptors $GABA_A$-α_1 and recombines sub-units $\alpha_1\beta_1\gamma_2$ or $\alpha_1\beta_1\gamma_3$ or $\alpha_1\beta_3\gamma_2$ and other sub-

units containing -α_1.[33,34] If the dentist decides to use alprazolam, its MDR is 0,50-0,75mg and is associated to a maximum tranquillizer effect after 2 hours[35] of the dose and length of 3-5 hours. The pharmacokinetics of the alprazolam delays the start of the tranquillizer effects and prolongs the length of its action. That makes this medication less indicated in dentistry but usually prescribed for treating generalized anxiety disorders, fibromyalgia, panic attacks. The alprazolam acts on sub-units -α_3, -β_1 and -Υ_2 and on receptors $GABA_A$-α_2 and $GABA_A$-Υ_2 located on hippocampus and amygdala producing tranquillizer effects and regulating stress response.[36] Triazolam, alprazolam, brotizolam and clonazepam have different pharmacokinetics and pharmacodynamics compared to lorazepam. They are not indicated for co-enteral conscious sedation. The half-life elimination of those drugs can vary between 2 and 10 hours ($t_{½}\beta$ = 10-12 hours).[37] Triazolam and alprazolam, if administered the day before the dental treatment, give low plasmatic concentrations, which are not satisfactory for the induction of the co-enteral sedation. The gastro-enteral administration, compared to the nasal [38] administration for example, allows 91-95% [39] of the drug availability, hence the 2mg dose of the night before the treatment will satisfy the induction's requirement. The dentist needs to know that lorazepam's absorption (both first and second dose) even if it is slower in reaching the pick, acts quicker due to its low levels of lag-time and half-life of absorption. Concentration's picks and effects depend on the dosage. The 2mg enteral dose the day before the treatment corresponds to a plasmatic concentration of 16,9 μg/ml.[40]

The two doses of 1 and 2mg provide tranquillizer effect prior, during and after the treatment, for 8 hours or more. The tranquillizer effects of lorazepam are explained with it being an agonist of receptors $GABA_A$--α_2 and $GABA_A$--α_3, without causing drowsiness or hypnosis effects. Lorazepam is only partially an agonist of receptors $GABA_A$-α_1 and -α_5 so it cannot cause drowsiness and hypnosis. At the above dosage it cannot cause psychomotor, cognitive or memory impairments that other drugs can cause.[41] It also provides muscle relaxation, retrograde amnesia of unpleasant memories. Being post-op effects like the ones given in intravenous sedation, the patient needs to be taken home by another person.[42] The co-enteral conscious sedation with lorazepam provides tranquillizer effects given by the addition of the two doses. The effects consist in different tranquillizer effects produced by an enteral dose of 1mg or less.[43]

If the tranquillizer effects are not satisfactory, an additional dose of CDDZ (gastro-enteral administered and titrated depending on the VAS scale result) is required. The use of CDDZ is justified by its short lag time, which explains the tranquillizer effects provided within few minutes after the gastro-enteral administration. The lag-time is the time that the drug takes to appear in the plasma, which is 4,2 minutes.[44] In table 3 CDDZ doses are decreasing for increasing levels of VAS scores. [45]

Finally, if after the two doses of lorazepam the patient's VAS score is 4.0, the CDDZ dose will be 1,07 mg. If the VAS score is 6.0, the CDDZ dose will be 0,88mg (table 3).

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Referee

***** Sedation in Dentistry. The use of drugs with tranquillizer properties in order to reduce anxiety during the treatment. Those drugs are called tranquillizers. They act depressing the central nervous system.

** Conscious sedation in Dentistry. Technique bases on the use of drugs with depressing effect on the central nervous system without loss of consciousness.

*** Enteral conscious sedation. Technique which utilizes drugs enteral administered acting depressing the central nervous system where verbal contact is intact.

**** Co-induction technique. (Tecnica che utilizza più farmaci per indurre una depressione del CNS.)

***** Co-enteral conscious sedation. Technique utilizing different drugs, enteral administered in several doses. Those drugs are titrated and act depressing the central nervous system. Verbal contact with the patient is intact.

******Co-enteral sedation. Technique utilizing drugs with hypnotic and tranquillizer properties, producing depression of the central nervous system during which verbal contact is impaired.

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