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Diazepam – its use in captive bottlenose dolphin (*Tursiops truncatus*)

Diazepam pharmacology:

Diazepam is a *Schedule IV* controlled drug under the international Convention on Psychotropic Substances. It should not be available without prescription.

Diazepam is a benzodiazepine drug that is available as a generic preparation but it is also sold under more than 500 different trade names, including: Valium®, Dialar®; Diazemuls®; Rimapam®; Stesolid®; Tensium® and Valclair®. Other drugs of the benzodiazepine group used in veterinary medicine include: midazolam (Hypnovel®); chlordiazepoxide (Librium®); lorazepam (Ativan®); clonazepam (Klonopin®); and alprazolam (Xanax®). These medications affect the central nervous system (CNS) potentiating the effects of GABA by binding to the benzodiazepine site of the $GABA_A$ receptor in the brain. GABA is a major inhibitory neurotransmitter in the brain. Research in rats shows that diazepam acts as a calcium ion channel blocker decreasing neuronal activity, thereby producing a depression of the CNS. It also inhibits acetylcholine release in the hypocampal synaptosomes of the brain, decreases histamine turnover in the brain; and decreases prolactin release (a hormone not only involved in milk let down and the development of behaviour (especially the mother / child bond), but also in the development of cells and the immune system). The depression of the limbic system, thalamus and hypothalamus that is produced by the benzodiazepines results in a reduction of anxiety, stress and fear. Diazepam has both a calming and amnesic effect on the patient and may make them sleepy, though it provides very poor sedation. This CNS depression has also enabled this drug to become important in the treatment of seizures and of musculature spasm. This benzodiazepine's fast-acting effects usually begin within 30 minutes to 2 hours of oral administration: resulting in some sedation, muscle relaxation, and greatly reduced fear and anxiety.

Almost all the research into diazepam and the benzodiazepines has been done in other species. But, there is little reason to suggest that the overall effects of diazepam should be markedly different in cetaceans. However, there is one major dissimilarity: it has been demonstrated that bottlenose dolphins can sleep in one hemisphere of the brain at a time while keeping the other side awake, and that this can be switched from one side of the brain to the other. The mechanism for how this works is still under investigation. Though perhaps not so common in mammals, unihemispheric sleep has been demonstrated in other animals, such as some birds. Un-anaesthetised dolphins have only been shown to have short periods of bihemispherical sleep so it is likely that unihemispheric sleep is important. It may be a way of keeping themselves alert, orientated and able to maintain progress within the ocean. Diazepam has been shown to induce unihemispheric slow waves in bottlenose dolphins, an important feature of unihemispheric sleep. This significant difference between dolphins and most other mammals may affect the outcomes of diazepam administration (and that of the other benzodiazepines) in these animals. As such, the results of diazepam administration in the bottlenose dolphin may prove less predictable than in other mammals, and this should raise a special note of caution in this species, as well as in other cetaceans.

When used appropriately, and under veterinary supervision, the benzodiazepines are very useful medications facilitating the handling of dolphins for certain procedures, such as diagnostics and transport. They have proved safe and effective when properly used.

Effects achieved at differing dosages:

- At low doses, benzodiazepines ramp down excessive behaviour and reduce excitability.
- At moderate doses, benzodiazepines reduce anxiety, may increase friendly and interactive behaviour.
- At high doses, benzodiazepines produce sedation, including incoordination, impaired thinking, and disorientation. They also produce sleepiness and in some animals may cause vomiting.
- Repeated use will cause some to become refractory and the drug to become increasingly addictive

Clinical usage of diazepam in the bottlenose dolphin:

- Diazepam (Valium® and generics) is the most commonly used sedative/tranquillizer in the bottlenose dolphin. It may be given by injection or per rectum, but is most frequently given orally. (Midazolam is a similar and often used as a more potent drug, however it has to be delivered by injection, and it is much more expensive and of shorter duration). Diazepam is used to produce light sedation, such as in the handling of trained dolphins to help keep them still and reduce stress during diagnostic investigation and treatment. They have also been used to sedate animals during capture and transport in order to reduce stress.
- Diazepam is inexpensive and relatively easy to acquire. It is quick acting when given *intravenously, intramuscularly, per os,* or *per rectum* and, for a benzodiazepine it is relatively long acting.
- The above attributes make diazepam an important medication in the management of cetaceans in captivity. It is the drug of first choice for many. Diazepam is usually given at the following rates: 0.1-0.2 mg/kg *intramuscularly* or 0.25-1.0 mg/kg *per os*. The larger doses should be reserved for research purposes only, or for extreme cases where animals have become refractory to the lower doses of oral diazepam.
- Several medicines interact with diazepam. Of particular importance are the antacids commonly administered in dolphinaria as a treatment/preventative for gastric ulceration that may itself be a consequence of stress. Antacids such as cimetidine and omeprazole inhibit the elimination of diazepam and thereby prolong its action and increasing the risks of toxicity.

Because of its potency and the potential for unwanted side effects, the reversing agent, flumazenil (Anexate®) should always be available whenever diazepam is used.

Side effects of the benzodiazepines:

- Benzodiazepines can cause amnesia and confusion especially at higher dosages, interfering with learning and memory. They may also have a negative impact on coordination and balance. Therefore, they are not good choices for long-term use with training and behaviour modification. If a benzodiazepine is required because of excessive anxiety or fear, it is best used under veterinary supervision and specifically for that purpose, with the dosage being gradually discontinued.
- Benzodiazepines can also have paradoxical effects including:
    - Reduced inhibition. This means that although the animal may not react as quickly to a frightening or disturbing event, should it react it might behave aggressively, even flying into a rage. The use of benzodiazepines is therefore inappropriate in the treatment of aggression. In humans, diazepam has also increased the incidence and seriousness of self-harm in some individuals. *(NB: I am particularly concerned that the inappropriate use of benzodiazepines may have contributed to the reportedly aggressive, and sometimes 'suicidal' behaviour of cetaceans in captivity)*
    - The animal might also become more excitable and unpredictable which in turn will make it difficult to manage

    - Increased appetite
    - Suppression of REM sleep. Sleeplessness may seem contradictory, but the benzodiazepines can actually produce increased anxiety in some animals. Although not common, this side effect seems to occur most often when the medicine is given after the animal has already begun to show signs of anxiety
- Benzodiazepines are metabolized in the liver and excreted through the kidneys. Therefore, care should be taken with these medicines as it has been noted that in cats, liver failure can occur as a result of using diazepam. If used repeatedly in the dolphin blood samples should be regularly taken to assess liver and kidney function
- Diazepam should not be used in pregnant or nursing females as the drug may adversely affect the foetus or the neonate.
- Long-term usage results in drug tolerance, ensuring that higher and higher doses are needed to achieve the same effects
- In humans, it has been demonstrated that after long-term usage the cognitive defects caused by diazepam can last for six months or more after the withdrawal of treatment
- Lastly, benzodiazepines can cause addiction. This can occur relatively quickly, for example if diazepam is given many times a day for more than four weeks. If diazepam has been used for some time it is important not to suddenly stop giving the medication as this may lead to withdrawal symptoms, including a rebound anxiety that may be worse than the original anxiety for which it was being used. Animals that have become addicted to diazepam MUST be gently weaned off the drug.

Potential for misuse:

The profound effects and ready availability of diazepam, including the possibility of supplies via the 'black market', means that there is a high probability that the drug may be misused and abused. That it may be acquired and used without documentary evidence also means that its usage may be easily hidden.

It is very tempting to use these medications as a management tool. They can be used to help mask the problems of poor husbandry, and of inappropriate and depauperate environments. Diazepam and the benzodiazepines reduce nervousness, stereotypies, and aggression all recognised as common problems in dolphinaria. The effects may be profound, but go unnoticed by the general public who are oblivious to such practices. As can be seen from the above, these drugs have potentially significant side effects interfering with learning, and aggravating aggression and self-harm. They can also interfere with sleep patterns. There is no place for the long-term use of diazepam (and the other benzodiazepines) in the management of bottlenose dolphins in captivity, nor is its long-term use of any benefit to the conservation of the species.

Summary:

Diazepam is properly used in dolphins as a sedative, anticonvulsant, and to temporarily treat certain behaviour disorders, such as anxiety. It may also be used for its effect of relaxing both skeletal muscles (muscles used in movement) and smooth muscles (muscles of the digestive system and urinary bladder), Diazepam may also have some action as an appetite stimulant.

However, diazepam has well documented side effects in a wide range of species. Therefore, its use in dolphinaria should be given serious consideration, and it should only be used with caution. In particular diazepam must be used with extreme caution in animals that are aggressive, or have liver disease (which may increase the drug's toxicity). Diazepam should not be administered to pregnant animals as it may cause birth defects, such as floppy baby syndrome, and interfere with the development of the nursing neonate.

Diazepam also lowers memory scores and reduces coordination, which in turn means that it is not suitable for use as a training aid and when dolphins are given moderate to higher levels of diazepam they will not perform or learn efficiently. Furthermore, aggression may be exaggerated. As a result diazepam is specifically contraindicated in the long-term treatment of behavioural disorders.

There is considerable potential for diazepam to be misused and the welfare of animals compromised. It may be used to help cover up serious deficiencies in management and husbandry, and there is strong evidence of it being misused in dolphinaria. In my opinion, diazepam has no legitimate place in the long-term management of cetaceans. If an animal(s) cannot be satisfactorily managed without sedation it should either be moved to a facility that can look after its welfare appropriately, or euthanized. Serious questions need to be asked of those institutions that misuse diazepam, and the withdrawal of their licenses considered.

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