DIAZEPAM RECTAL TUBES

EXPERT REPORT ON PHARMACO-TOXICOLOGICAL DOCUMENTATION

[redacted] CP Pharmaceuticals Ltd.

1 Pharmacodynamics

Diazepam is a psychotropic substance from the class of 1,4-benzodiazepines with marked properties of suppression of agitation and anxiety as well as sedative and hypnotic effects. In addition, diazepam demonstrates muscle relaxant and anticonvulsive properties.

Diazepam binds to specific receptors in the central nervous system and particular peripheral organs. The benzodiazepine receptors in the CNS have a close functional connection with receptors of the GABA-ergic transmitter system. After binding to the benzodiazepine receptor, diazepam augments the inhibitory effect of GABA-ergic transmission.

Diazepam can be used in the short-term treatment of anxiety and tension states, as a sedative and premedicant, in the control of muscle spasm and in the management of alcohol withdrawal symptoms.

2 Pharmacokinetics

The pharmacokinetic parameters of diazepam show wide interindividual variation.

2.1 Absorption

After rectal administration of the solution, diazepam is absorbed rapidly and almost completely from the rectum.

The onset of the therapeutic effect occurs within a few minutes of rectal administration and is more rapid with the solution than with suppositories. The rapidity of the rise in the serum level following rectal administration corresponds approximately to that following an intravenous dose but peak plasma concentrations are lower after rectal tubes than after intravenous administration.

In adults maximal plasma concentrations following the administration of 10 mg diazepam in rectal solution are reached after about 10 - 30 minutes (ca. 150 - 400 ng/ml) and following administration of suppositories after about 30 - 120 minutes (Hefting et al 1992; Moolenaar et al 1980; Moolenaar 1989). Occasionally adsorption to the faeces in the rectum can affect absorption (Magnussen et al 1979).

2.2 Protein binding/volume of distribution

The plasma protein binding of diazepam is between 95 - 99%; in patients with impaired liver or kidney function, lower levels of binding are present.

The volume of distribution is between 0.95 - 2 l/kg body weight depending on age.

2.3 Metabolism and elimination

Diazepam is metabolised mainly in the liver. Its metabolites, N-desmethyldiazepam (nordiazepam), temazepam and oxazepam, which appear in the urine as glucuronides, are also pharmacologically active substances. Only 20% of the metabolites are detected in the urine in the first 72 hours.
The active metabolites have the following plasma half-lives:

N-desmethyldiazepam	30 - 100 hours
temazepam	10 - 20 hours
oxazepam	5 - 15 hours.

Following repeated doses of diazepam, the N-desmethyldiazepam fraction predominates with wide interindividual variation. This main metabolite has a longer terminal half-life than diazepam itself.

With chronic diazepam treatment, the elimination is further prolonged and the serum level of the main metabolite becomes therapeutically relevant due to accumulation.

Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days. Excretion is mainly renal and also partly biliary; it is dependent on age as well as hepatic and renal function.

Metabolism and elimination in the neonate are markedly slower than in children and adults. In the elderly, elimination is prolonged by a factor of 2 to 4. In patients with impaired renal function, elimination is also prolonged. In patients with hepatic disorders (liver cirrhosis, hepatitis), elimination is prolonged by a factor of 2.

2.4 Penetration into the cerebrospinal fluid

Diazepam is lipophilic and penetrates quickly into the cerebrospinal fluid together with its active metabolite N-desmethyldiazepam.

2.5 Transplacental passage and lactation

Diazepam and its main metabolite, N-desmethyldiazepam, cross the placental barrier and are secreted into the breast milk. Diazepam accumulates in the foetal compartment and can reach a level in the neonate of three times the maternal serum concentration. In premature babies, the elimination is considerably prolonged due to immature hepatic and renal function and this can be as long as 10 days. If diazepam is administered before or during birth or if the mother has been given multiple large doses, Apgar values are significantly reduced both in premature and term neonates; the incidence of hyperbilirubinaemia is significantly increased and extensive oedema and muscular hypotonia may be observed for up to four days post-partum.

3 Toxicity

The toxicological properties of diazepam are well known and have been extensively reviewed by Hines (1981), therefore no toxicological studies are provided on the substance itself. However, the product under discussion is intended to be administered rectally as opposed to orally or parenterally; evidence for local tolerability is provided in four animal studies, these are summarised below.

* The formulation of the vehicle and the diazepam rectal solution (Stesolid, Dumex) used in these studies were the same as those of the product which is the subject of this application.

3.1 Single dose tolerability studies

A single application into the conjunctival sac of the right eyes of six rabbits of 0.1 ml of diazepam rectal solution (Stesolid 10 mg, Dumex) vehicle* alone did not cause irritation (maximal irritation value according to Draize = 1.5) (Neumann and Leuschner 1981a).

A single application into the conjunctival sac of the right eyes of six rabbits of 0.1 ml of diazepam rectal solution 4mg/ml (Stesolid 10 mg, Dumex)* did not cause irritation (maximal irritation value according to Draize = 0.6) (Neumann and Leuschner 1981b).

3.2 Repeat dose tolerability studies

3.2.1 Local tolerance study: 14-day application to the eyes in the rabbit (Neumann and Leuschner, 1981c)

Six white Russian rabbits (3 male, 3 female) were given 0.1 ml diazepam rectal solution 4mg/ml (Stesolid 10 mg, Dumex)* and another six rabbits were given 0.1 ml of the vehicle alone once daily into the conjunctival sac of the right eyes for 14 days. A control group of six rabbits received saline.

Both solutions were well tolerated.
Erythema of the conjunctivae at reaction level 1 according to Draize was observed in all animals in the diazepam treated group and in five animals in the vehicle group. From the ninth day, this was seen in only a few rabbits and by the end of the study it had disappeared.

The cornea and iris showed no substance-related changes. There was no conjunctival swelling or hypersecretion. Macro- and microscopic examination of the whole eye, the conjunctival mucosa, nose and lacrymal ducts revealed no pathological findings.

Behaviour, appearance and faeces were normal. No systemic reactions or changes during macro- or microscopic examination were observed. No animals died during the study.

3.2.2 Local tolerance study: 7-day rectal administration to the dog (Neumann and Leuschner 1981d)

Diazepam rectal solution 4mg/ml (Stesolid 10 mg, Dumex)* was administered once daily

(6 ml) to six beagle dogs (3 male, 3 female) for seven days. A control group received 6 ml normal saline rectally.

Sedation was observed in all the dogs receiving diazepam approximately 30 minutes after instillation and lasting for one hour on each day of treatment.

There were no changes in the appearance of the faeces; no intercurrent infection was observed; no dog died prior to termination of the study; there was no effect of treatment on body weight; no pathological substance-related changes were reported either macroscopically or microscopically after examination of the anal mucosa and rectal ampulla.

3.3 Toxicity in humans

3.3.1 Acute toxicity in humans

Diazepam-induced disease seems to be exceptional; there is no sound evidence of haematological, hepatic or renal toxicity; no significant alterations in thyroid or pituitary functions, urinary excretion of catecholamines, prolactin or blood glucose levels have been observed. Hypersensitivity reactions to diazepam itself are extremely rare and there are no reports of hypersensitivity to Stesolid Rectal Tubes over 12 years of clinical use.

Acute toxicity is generally limited to transient and mild dose-related neurological and neuromuscular side effects (Hines 1981; Schmidt 1989).

3.3.2 Local tolerability in volunteers (Hansen et al 1989)

The extent of local irritation was studied in 24 healthy adult volunteers in a randomised, triple cross-over design by applying 10 ml diazepam rectal solution (Stesolid, Dumex)* v. 2.5 ml diazepam rectal solution (Stesolid, Dumex)* v. 2.5 ml vehicle.

A burning or stinging sensation lasting up to 15 minutes was reported in 60% of subjects immediately after 10 ml administration, in 12% after 2.5 ml administration and 0% after vehicle administration. Endoscopic assessment 24 hours after instillation showed mechanical irritation in two subjects given 10ml and one given 2.5ml and local irritation in two subjects given 10ml and one each after 2.5ml and the vehicle. Control endoscopy seven days after administration revealed no pathology. The irritation appears to be volume related and it might be expected to affect between 12 and 60% of patients given the usual dose. Slight local irritation may be advantageous in causing hyperaemia and therefore more rapid absorption.

3.4 Chronic toxicity

Diazepam Rectal Tube is not intended for long-term treatment. Rectal instillation of diazepam is recommended if intravenous or oral administration is impossible, difficult or not appropriate.

Studies in animals have indicated no evidence of drug-induced changes and there are almost no reports concerning the chronic toxicity of diazepam. After prolonged oral

intake, a brown colouration of the ocular lens has been observed but it is doubtful that this is drug-related (Pau, 1985). Dependency may develop with the chronic or repeated use of diazepam even after daily use for only a few weeks. This applies at therapeutic doses as well as higher doses but is unlikely with this particular formulation if used as directed.

Diazepam may occasionally increase growth hormone and testosterone levels and might have a variable effect on appetite and weight.

3.5 Carcinogenic and mutagenic potential

There are no long-term animal studies to investigate the carcinogenic potential of diazepam.

Several investigations pointed to a weakly mutagenic potential at doses far above the human therapeutic dose.

3.6 Reproductive toxicity

In humans it would appear that the risk of congenital abnormalities from the ingestion of therapeutic doses of benzodiazepines is slight, although a few epidemiological studies have pointed to an increased risk of cleft palate. There are case reports of congenital abnormalities and mental retardation in prenatally exposed children following overdosage and intoxication with benzodiazepines.

From animal studies the following observations have been made. In the mouse, cleft palate occurred after prenatal exposure to diazepam. In the hamster, in addition to cleft palate, exencephaly and limb deformities were seen after very high prenatal doses. In rats and primates, diazepam was not teratogenic. Animal studies have given indications of behaviour disturbances in the offspring of chronically exposed dams. In mice, anomalies of the heads of spermatozoa were observed after treatment for one to six weeks.

4 Conclusions

Indications

Diazepam Rectal Tubes offer the possibility of safety and efficacy of administration of diazepam when the anticonvulsant, sedative and muscle relaxant properties of diazepam are required. Diazepam Rectal Tubes may be used in severe or disabling anxiety and agitation; epileptic and febrile convulsions; tetanus; as a sedative in minor surgical and dental procedures, or other circumstances in which a rapid effect is required but where intravenous injection is impracticable or undesirable. Diazepam Rectal Tubes may be of particular value for the immediate treatment of convulsions in children.

Contraindications and precautions

Contraindications against the use of Diazepam Rectal Tubes are those for diazepam itself, ie. hypersensitivity to benzodiazepines, myasthenia gravis and severe respiratory

insufficiency. In addition, Diazepam Rectal Tubes should be used with caution in patients with renal or hepatic dysfunction, chronic pulmonary insufficiency, closed angle glaucoma or organic brain changes, particularly arteriosclerosis.

Diazepam should not be used in pregnancy or lactation unless the benefit is considered to outweigh the risk. Use near the end of pregnancy or during labour can be associated with hypothermia, hypotonia, respiratory depression and poor suckling in the neonate.

As with other benzodiazepines extreme caution should be used if prescribing diazepam for patients with personality disorders. The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who are depressed or show aggressive behaviour towards self and others.

Diazepam can affect the reaction capacity sufficiently to impair the ability to drive and operate machinery; this effect is potentiated by the concurrent intake of alcohol.

Dependence potential

Tolerance and dependency may develop with the chronic or repeated use of diazepam even after daily use for only a few weeks. This applies not only to abuse involving particularly high doses but also to usage in the normal therapeutic dosage range but it is not likely with this formulation if used as directed.

Side effects

The safety profile of oral diazepam is well known. Similar systemic adverse experiences have been reported with use of the Diazepam Rectal Tube. Local tolerability of the product was found to be excellent in the preclinical, clinical and post-marketing evaluations.

The side effects of diazepam are usually mild and infrequent. The most common side effects are sedation, drowsiness, headaches, muscle weakness, dizziness (with risk of falls in the elderly), ataxia, confusion, slurred speech, tremor, numbed emotions, reduced alertness, fatigue, double vision, anterograde amnesia and a hangover effect. Elderly or debilitated patients are particularly susceptible to side effects and may require lower doses. Other effects which may occur rarely are dry mouth, increased appetite, gastrointestinal and visual disturbances, jaundice, urinary retention, hypotension, bradycardia, changes in libido, menstrual disturbances, skin reactions, blood dyscrasias, laryngeal spasm, chest pain, respiratory depression and apnoea.

In susceptible patients, an unnoticed depression may become evident. Paradoxical reactions (restlessness, agitation, irritability, rages, hallucinations) are known to occur with benzodiazepines and are more likely to occur in children and the elderly.

Side effects are generally reversible on reduction of the dose and can usually be avoided by individual tailoring of the dose.

Overdosage

The symptoms of mild overdose may include confusion, somnolence, ataxia, dysarthria, hypotension, muscular weakness. In cases of severe overdose, depression of vital functions may occur, particularly the respiratory centre (respiratory and circulatory depression, cyanosis, loss of consciousness progressing to the development of respiratory and cardiac arrest). As drug levels fall severe agitation may develop. Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function. Flumazenil is indicated to counteract the central depressive effect of benzodiazepines.

Overall conclusion

Diazepam is a well known compound with an established efficacy and safety profile. The absorption of diazepam from the rectal solution is rapid and almost complete leading to therapeutic plasma levels within minutes of an appropriate dose. (see Clinical Expert Report). There may be some local irritation with rectal administration in 12 - 60% of patients given the recommended dose.

In my opinion the pharmacodynamics, pharmacokinetics and toxicity of diazepam support its administration as a rectal solution for use in the indications and at the dosage proposed for Diazepam Rectal Tubes.

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Signature of Expert

Place, date

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