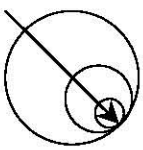
MODULE 2.5

CLINICAL OVERVIEW

on the clinical documentation of

Diazepam Desitin®
rectal solution 5 mg / 10 mg



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List of abbreviations

ATC	Anatomic Therapeutic Group
AUC_{0-t}	area under the time plasma concentration curve from administration to last observed concentration at time t
CAS	Chemical Abstracts Service
CI	confidence interval
Cmax	maximum drug concentration in plasma / serum
CNS	central nervous system
CYP (P450)	cytochrome (P450)
FDA	(US) Food and Drug Administration
EEG	electroencephalogram
GABA	γ-aminobutyric acid
$GABA_A$ (receptor)	A-type γ-aminobutyric acid receptor
GFR	glomerular filtration rate
h	hour(s)
ICU	Intensive Care Unit
i.v.	intravenous
kg	kilogram (body weight)
L	litre
mg	milligram
µg	microgram
mL	millilitre
mmHg	millimetre(s) mercury
Tmax	time to maximum drug concentration
UK	United Kingdom
v/v	% volume per volume

2.5 Clinical overview

This document is intended to provide a critical analysis of the clinical data available to assess the efficacy and safety of Diazepam Desitin® rectal solution 5 mg / 10 mg, a medication marketed by Desitin Arzneimittel GmbH, Hamburg, for the following indications:

- patients with epileptic and febrile convulsions;
- relief of muscle spasms, e.g. caused by tetanus
- sedation in minor surgical and dental procedures;
- initial use in anxiety and agitation when the disorder is severe, disabling or subjecting the individual to extreme distress.

Diazepam Desitin® rectal solution is a non-sterile solution formulation containing 5 mg or 10 mg diazepam as the only active ingredient; the vehicle used is a water / ethanol (12% v/v) / propylene glycol mixture, which is similar to that of the parenteral solution. The aqueous alcoholic solution (2.5 mL) is provided in pre-filled, unit-dose tubes that allow simple and easy administration by the rectal mucosal route. The rectal formulation is used to achieve rapid systemic effects when a rapid onset of action is required and when establishing an intravenous line is difficult, delayed or undesirable.

Active principle and excipients present in this formulation are well-known and documented. Diazepam has been used for almost half a century in the above and further indications and still is one of the most widely prescribed benzodiazepines. As other representatives of this class, diazepam mainly acts on the CNS by enhancing GABA-ergic actions with a favourable safety profile. Its most prominent effects are sedation, hypnosis, decreased anxiety, muscle relaxation, and anticonvulsant activity. The terminal disposition half-life of diazepam is relatively short; the major active metabolite, N-desmethyldiazepam, has a longer elimination half-life than the parent compound and is responsible for the prolonged duration of action.

Due to the long-standing experience with diazepam in the above indications and the fact that the bioavailability of diazepam from Diazepam Desitin® rectal solution can be reliably predicted on the basis of available data, it is justified that the clinical documentation of Diazepam Desitin® rectal solution solely relies on published scientific evidence. With the exception of a bioavailability study, no clinical studies were performed by the applicant nor are further studies deemed necessary to assess the efficacy and safety of the present formulation and the active ingredient, diazepam. Medline and other publicly available databases were searched to identify relevant up-to-date information.

Most publications on diazepam administration by the rectal route relate to investigations performed with sterile, undiluted diazepam solutions intended for parenteral use, e.g. the i.v. solution of Valium® compounded with 10% ethanol and 40% propylene glycol. Until recently, no diazepam formulation specifically licensed for rectal administration had been available in many countries (e.g. in the United States). Therefore, physicians treating seizures had devised a variety of techniques for rectal application of diazepam in order to ascertain a rapid onset of action under circumstances when a parenteral administration was not applicable. In Australia, a position statement on the use of rectal diazepam, mainly in a paediatric population, was issued in 1995 to define the indications and mode of its use. [1]

2.5.1 Product development rationale

2.5.1.1 Identification

Diazepam belongs to the class of 1,4-benzodiazepines. The chemical name of diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one or 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one; its molecular weight is 284.75, the molecular formula $C_{16}H_{13}ClN_2O$. The structural formula is represented in Figure 1. Diazepam is a white or yellow, odourless crystalline powder. It has a very slight solubility in water only, but is soluble in alcohol and freely soluble in chloroform.

In the ATC classification diazepam is listed under N05 (psycholeptics), subgroups N05B (anxiolytics) and N05BA (benzodiazepine derivatives), or N03 (antiepileptics), subgroup N03AE (benzodiazepine derivatives). Its CAS-Registry number is 439-14-5.

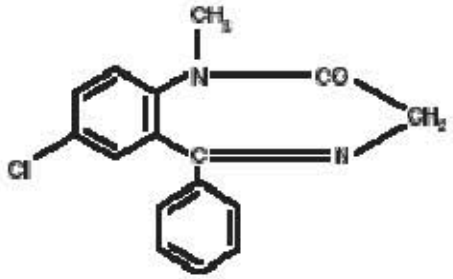

Figure 1 Structural formula of diazepam

Diazepam Desitin® rectal solution is intended for use in patients with diazepam-responsive conditions (e.g. epileptic and febrile convulsions or muscle spasms of various origin), when a rapid onset of action is required and intravenous access is not possible or undesirable. Diazepam Desitin® rectal solution may further be used as a sedative in minor surgical and dental procedures or early in anxiety and agitation when the disorder is severe, disabling or subjecting the individual to extreme distress. Diazepam Desitin® rectal solution revealed to be particularly useful for the immediate treatment of convulsions in children due to the non-invasiveness of the procedure compared with i.v. injection.

2.5.1.2 Use in seizures

Diazepam, lorazepam, phenobarbital, phenytoin and paraldehyde are all regarded as drugs of first choice in the treatment of acute tonic-clonic (grand mal) convulsions and convulsive status epilepticus (seizure activity lasting longer than 30 minutes, or recurrent seizures in so close sequence that no period of consciousness occurs between ictal periods). These conditions are medical emergencies and demand urgent and appropriate anticonvulsant treatment. Usually the i.v. route is preferred. However, in many cases establishment or maintenance of an i.v. line may reveal difficult or is undesirable; in these circumstances, the rectal route is an appealing alternative. Early control or termination of seizure activity using the rectal route prevents or mitigates permanent neurologic damage and may reduce the need for more aggressive interventions (e.g. administration of multiple anticonvulsants, endotracheal intubation, and ICU admission). Indeed, the chances of successful response to a single medication are lessened, if treatment is delayed.

Moreover, Diazepam Desitin® rectal solution may also be a useful adjunct to standard anti-epileptic treatment in patients suffering from so-called serial, cluster, or acute repetitive seizures; these are observed in some patients and represent epileptic seizure recurrences for minutes or hours that occur periodically and follow a distinctive temporal pattern.

Prompt and effective medical intervention is also a treatment priority in any seizure during childhood, except those of short duration. Due to its easy administration and quick onset of action, Diazepam Desitin® rectal solution is of particular value for the immediate treatment of epileptic or febrile convulsions and seizures in children that represent the most frequent non-traumatic pre-hospital complaint in patients less than 18 years old. Rectal diazepam is the most commonly used medication before admission to the hospital in the UK. [2]

Prophylaxis of febrile seizures with anti-epileptics has largely been abandoned and is no more recommended. According to epidemiological data from major cohort studies, the long-term outcome for most children with febrile convulsions and seizures is far better than previously assumed. This was confirmed by the long-term follow-up (12 years) of a cohort of 289 children randomised during early childhood to either intermittent seizure prophylaxis or no prophylaxis (treatment during febrile seizures only). [3] Neither benefits nor adverse effects were associated with febrile seizure prophylaxis using rectal diazepam as assessed on the basis of scholastic achievement, epilepsy occurrence, and assessment of neurological, motor, intellectual, and cognitive skills.

2.5.1.3 Relief of muscle spasms due to tetanus

Available evidence suggests that diazepam is also effective as an adjunct therapy for the relief of skeletal muscle spasm resulting from various pathologies (mainly tetanus, but also those related to a local pathology, by upper motor neuron disorders, spinal cord lesions, or multiple sclerosis).

The increase in active immunisation over the past decades has markedly reduced the incidence of clinical tetanus in developed countries; between 1984 and 1995, no more than 145 cases of tetanus occurred in England and Wales, 75% occurring in people over 45 years who did not benefit from postnatal immunisation. In developing countries, the disease remains a significant public health problem, because – once contracted – tetanus still carries a high mortality rate in the range of 15 to 20%. Surveys of the World Health Organisation (WHO) indicate that only 3% of neonatal tetanus is reported. A true global incidence of 700,000 to 1,000,000 cases per year is estimated. [4]

The clinical features of tetanus are due to the tetanus toxin which blocks the inhibitory action of GABA to motor neurons, resulting in typical muscle spasms (trismus, 'risus sardonicus', and opisthotonus). If mechanical ventilation is available, the most frequent causes of death in tetanus patients are autonomous dysfunction, various respiratory complications and cardiac arrhythmias.

Though diazepam has never been properly evaluated in randomised, controlled trials, diazepam remains the mainstay of tetanus treatment for nearly 40 years now since the first successful treatment by Weinberg in 1964. Since then the drug proved adequate to interrupt the violent muscular spasms and recurring convulsions in tetanus disease, both in adults and children. [5,6] Thereby, the frequency of complications and mortality has been reduced.

2.5.2 Overview of Biopharmaceutics

A bioavailability / bioequivalence study to characterise the pharmacokinetic behaviour of Diazepam Desitin® rectal solution has been performed by the applicant in healthy adult volunteers. [7] Moreover, extensive and concurring information is available on the pharmacokinetics of diazepam if rectally administered as a solution and deemed adequate to define the pharmacokinetic labelling of Diazepam Desitin® rectal solution in the above indications. Excipients used in the literature are essentially similar to those used in the present formulation.

2.5.2.1 Absorption after rectal transmucosal administration

It is generally accepted to administer selected medications by the rectal mucosal route for systemic effects if other routes are not available, impracticable, or undesirable. Relevant factors influencing the speed and extent of absorption of drugs by this route are the formulation, rectal intraluminal pH,

presence of rectal contents, the volume of fluid, the concentration administered, and the site of drug delivery (low / high in the rectum).

For a solution of diazepam rapid and complete bioavailability of the drug after rectal administration has been unanimously reported, the rate and extent being similar to that after intravenous and also oral application. [8,9] The rectal application is distinctly more effective than either diazepam suppositories or i.m. diazepam injections: these were both shown to be unsuitable and inadequate in acute seizures; indeed, suppositories are characterised by a delayed and erratic systemic input of diazepam due to a longer time to liquefaction; similarly, the systemic bioavailability of diazepam after i.m. administration was shown to be slow and unpredictable.

The volume of the rectally administered solution (2.5 mL) is small enough to be retained in the rectal vault. Rectal pH may influence drug uptake by altering the amount of drug that is ionised. Based on the low ionisation constant of 3.3, negligible dissociation of diazepam can be assumed at the usual pH of the rectal vault in adults and children of > 7.0. [10] This together with its high lipid solubility and the concentration gradient achieved by the 0.4% / 0.2% solution explains why diazepam from Diazepam Desitin® rectal solution readily moves across the rectal mucosa by a process of passive diffusion.

The pre-filled, unit-dose tubes deliver their content to the lower rectum which is drained by the inferior and middle rectal veins which drain into the inferior vena cava via the internal iliac vein; this avoids first-pass metabolism by the liver as occurs with administration in the upper rectum which is drained into the portal vein via the superior rectal vein. However, for low-clearance drugs such as diazepam, no dose adaptation is required.

Nevertheless, there is some between-patient variability in terms of both the rate and extent of bioavailability to about a similar extent as otherwise seen with the oral route of administration. [11] The most commonly reported pharmacokinetic input failures relate to incomplete administration (dead space of the device used) or expulsion or adsorption by faeces. However, in almost all clinical studies rectal diazepam was reported to have been effective without previous evacuation of faeces.

In humans, peak plasma concentrations after the rectal administration of a diazepam solution were reported within 10 to 30 minutes. [12] Therefore, compared with a bolus i.v. injection of diazepam, rectal diazepam may have a slightly slower onset of action (within 5 to 10 minutes versus 1 to 3 minutes after i.v. bolus injection), but a longer duration of action (20 to 30 minutes versus 10 to 20 minutes). [8,13,14]

Moreover, peak serum concentrations were slightly lower compared with i.v. bolus injections. The somewhat delayed systemic input and the lower peak concentrations result in better clinical safety and tolerability, while respiratory and cardiovascular depression occur less frequently than with i.v. bolus injections.

	peroral (tablet)	i.v.	rectal solution	suppository	i.m.
Cmax (ng/mL)	383	650	369	272	375
Tmax (min)	52	6	17	82	95

Table 1 Comparative absorption of diazepam 10 mg [14]

Rectal administration of diazepam is well tolerated and resulted in only limited and rapidly transient irritation of the rectal mucosa. Only in immuno-suppressed patients in whom small trauma could lead to the formation of an abscess, rectal administration should be avoided.

Thus, in all cases where a rapid and reliable onset of action is required, the rectal transmucosal route is convenient and an attractive alternative to i.v. administration of diazepam; this is particularly true in case of a medical emergency in children (e.g. status epilepticus), because an i.v. access is not required.

2.5.2.2 Bioavailability / bioequivalence study

In a study in 18 healthy adult subjects the pharmacokinetics of diazepam were evaluated after the administration of a single dose of 10 mg diazepam using three different formulations in a three-period cross-over design [7]:

- Diazepam Desitin® rectal tube (rectal route);
- Diazepam Desitin® injection solution (i.v. administration);
- Stesolid® rectal tube (rectal route).

Compared with the i.v. administration absolute bioavailability of diazepam from Diazepam Desitin® rectal tubes as measured on the basis of AUC_{0-72} was almost complete (85%; 95% CI [79-91%]). In agreement with reports in the scientific literature the maximum serum concentration was lower (31%; 95% CI [27-34%]), and the median time to C_{max} somewhat slower (30 min versus 10 min). Pharmacokinetic parameters for the main active metabolite, N-desmethyldiazepam, were essentially similar for rectal tubes and i.v. administration (AUC_{0-120} 3080 µg/L*h versus 3417 µg/L*h, C_{max} 34.4 µg/L versus 38.0 µg/L); terminal disposition half-life was slightly longer after use of Diazepam Desitin® rectal tubes (83.4 h versus 66.6 h).

Moreover, the ratios of the estimates of C_{max} and $AUC_{0-\infty}$ for diazepam and N-desmethyldiazepam from Diazepam Desitin® rectal tubes and Stesolid® rectal tubes were well within the usual acceptance interval of 0.80 to 1.25. Thus, the two preparations for rectal administration were shown to be bioequivalent with regard to the rate and extent of absorption.

2.5.3 Overview on Clinical Pharmacology

2.5.3.1 Pharmacodynamics

Diazepam readily penetrates the blood-brain-barrier due to its high lipid solubility, hence rapidly terminating epileptic or febrile seizures. Though the exact mechanism of action in the treatment of seizures is not fully elucidated, there is general agreement that the anti-seizure action of diazepam and other benzodiazepines is mediated by their interaction with the central type A γ-aminobutyric acid receptors ($GABA_A$). The resulting tighter binding of GABA to its $GABA_A$ receptors prevents excessive depolarisation of neurons and the generation and spread of seizures. More detailed information on this subject is available in the respective section of the preclinical summary.

While enhanced GABA activity can explain most of the CNS-related pharmacological effects of benzodiazepines, increased pre-synaptic inhibition at the spinal level is supposed to contribute to skeletal muscle relaxation. There also appears to be a direct peripheral action on the contractile process of muscles.

2.5.3.2 Pharmacokinetics

Available data from a pharmacokinetic study in healthy volunteers demonstrate that diazepam from Diazepam Desitin® rectal solution is rapidly and completely absorbed. [7] The rate and extent of absorption of diazepam from Diazepam Desitin® rectal solution was bioequivalent with another commercially available rectal preparation (Stesolid®); moreover, pharmacokinetic data are in agreement with those published in the scientific literature for extemporaneous rectal use of diazepam injection solution.

Absorption

Due to its high lipid-solubility and negligible dissociation diazepam from Diazepam Desitin® rectal solution is readily and completely absorbed after rectal administration in both adults and children. The rate of absorption is only slightly slower than with i.v. bolus injections and more rapid and reliable than with peroral or i.m. administration. [7,15,16] With the rectal route, peak serum levels typically occurred within 10 to 30 minutes. Suppositories in contrast have a more delayed and more variable systemic input of diazepam due to a longer time to liquefaction.

The serum levels of diazepam to be achieved for an anti-convulsant effect have not been established; in the literature a range from 0.15 to 0.50 µg/mL is cited. Because of the poor correlation between serum levels and clinical response, therapeutic drug monitoring is of limited clinical utility. Mean peak serum diazepam levels of 0.23 µg/mL were achieved after administration of a single dose (10 mg) of Diazepam Desitin® rectal solution. This is well in agreement with values reported in the literature of 0.31 and 0.39 µg/mL after rectal doses of 10 mg of solution in 9 epileptic patients and 9 healthy volunteers. [15,17] Compared with i.v. injection, no essential difference in the bioavailability of diazepam was observed with either i.m. injection, rectal administration of a solution using propylene glycol or polyethylene glycol as the main solvent or ingestion of tablets. [15,16]

No measurable first pass metabolism was observed and enterohepatic circulation is minimal.

Distribution

Due to its high lipid solubility, diazepam readily passes into the brain, and into other well-perfused tissues and organs with a subsequent redistribution into muscle and adipose tissue in a manner typical for highly lipid-soluble agents.

Due to its high lipophilicity diazepam crosses the blood-brain barrier and rapidly enters the cerebrospinal fluid. The concentration achieved corresponds to approximately 1.6% of the total plasma diazepam concentration. [18]

The volume of distribution of diazepam is about 1.1 L/kg (0.7 L/kg to 3.4 L/kg), depending on age, sex and constitution. The volume of distribution was higher in elderly male subjects compared with their younger counterparts, in young females compared with young males, and in obese patients as compared with normal-weight individuals.

Studies in healthy volunteers demonstrated that in the circulation, both diazepam and its major metabolite (desmethyldiazepam), are extensively bound to plasma proteins (>95%); the free fraction is 1.48% on average and was shown to increase with age. [19] Elderly patients and those with low serum albumin concentrations may therefore experience more pronounced CNS effects as a result of the larger fraction of free diazepam. Moreover, sex related differences in plasma protein binding of and diazepam were reported; in women taking oral contraceptives plasma concentrations of free diazepam were significantly higher than in females not taking contraceptives or men of similar age. [20]

Diazepam crosses the placental barrier to the foetus and is present in breast milk. Diazepam can be detected within seconds in neonatal blood (arterial and venous) following i.v. administration to the mother and equilibration of maternal and foetal blood levels occurs within about 10 minutes. [21,22] Passage of benzodiazepines across the placenta depends on the degree of protein binding in mother and foetus, which is influenced by factors such as stage of pregnancy and plasma concentrations of free fatty acids in mother and foetus.

Metabolism

Diazepam is predominantly metabolised by enzymes in the liver into two pharmacologically active metabolites; only very little unchanged drug is directly eliminated in the urine.

To date, in-vitro studies using human liver preparations have found that diazepam demethylation occurs via CYP1A2, CYP3A4, CYP2C9, and CYP2C19 isoenzymes of cytochrome P_{450}. No relevant inhibition of diazepam's biotransformation was found in the presence of selective inhibitors of CYP2A6, CYP2C9, CYP2D6, and CYP1A2, indicating that these enzymes play no relevant role in the metabolism of diazepam.

Hepatic N-demethylation involving mainly CYP2C19 and CYP3A4 results in the formation of the main active metabolite N-desmethyldiazepam, also known as nordiazepam. A minor active metabolite is N-methyloxazepam (temazepam). Both metabolites products are then converted to oxazepam which is conjugated with glucuronic acid before excretion. [23]

Therefore, at therapeutic doses the main active substances found in plasma are diazepam and desmethyldiazepam, while oxazepam and temazepam are usually not detectable because they are conjugated and excreted at almost the same rate as they are generated. [7]

The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 and CYP3A4. CYP 2C19 is known to exhibit genetic polymorphism; about 2 to 3% of the Caucasian population have little or no activity and are '*slow hydroxylators or metabolisers*' as compared to 15 to 25% of the Asian population.

Excretion

Diazepam clearance shows marked inter-subject variability. The disposition of the parent compound is bi-exponential with a first alpha-phase with a half-life of 7 to 10 h, followed by a second slower beta-phase with a half-life of 1 to 2 days. [24] Extensive hepatic metabolism occurs to active metabolites with less than 25% of the drug excreted unchanged in the urine.

Elimination of the active metabolites N-desmethyldiazepam (nordiazepam), N-methyloxazepam (temazepam), and oxazepam is significantly slower with half-lives of 30-100, 10-20, and 5-15 hours, respectively.

The half-life is prolonged in newborns, in elderly or obese subjects, and in patients with cirrhosis or hepatitis. It is shortened in patients taking drugs (including anticonvulsants) that induce hepatic CYP enzyme activity.

2.5.3.3 Metabolic interactions

No interactions studies have been performed with Diazepam Desitin® rectal solution, and reports in the scientific literature to evaluate the interaction of rectally administered diazepam with other drugs are scarce. Bibliographic references on interactions mostly refer to (chronic) peroral use, but also i.v. diazepam.

Diazepam itself does not induce or inhibit hepatic enzyme activity; there is also no evidence of autoinduction or -inhibition which would significantly alter its own metabolism with protracted therapy.

However, diazepam being a substrate for CYP2C19 and CYP3A4, it may potentially interfere pharmacokinetically with other agents metabolised by these isoenzymes by means of substrate

competition and displacement. Pre-treatment with diazepam slightly but significantly reduced the clearance of *ketamine*; this results in increased ketamine plasma levels associated with prolonged duration of anaesthesia and slow recovery following ketamine anaesthesia; this synergy might result from the pharmacokinetic reaction but also from additive pharmacodynamic properties (or both). [25] The plasma concentrations of *bupivacaine*, but not those of *lidocaine*, were significantly increased by premedication with a single 10 mg rectal dose of diazepam before minor surgery (hernia repair or orchidopexy). [26]

Furthermore, diazepam is sensitive to interaction with numerous agents that induce or inhibit hepatic CYP pathways or conjugation as its clearance is predominantly via hepatic biotransformation.

The following agents were shown to inhibit diazepam's metabolisation (prolongation of half-life, reduction in total body clearance, increase in peak and total exposure): cimetidine [27,28], omeprazol and its isomer (esomeprazole) but not other structurally related proton pump inhibitors [29], oestrogen-containing oral contraceptives [30], disulfiram [31], macrolide antibiotics [32], isoniazid [33], fluvoxamine [34], fluoxetine [35,36], azole antimycotics (ketoconazole, itraconazole, fluconazole) [37], propoxyphene [38], and ciprofloxacine. Competition for metabolism and/or inhibition of metabolism could result in an increased plasma concentration of diazepam. These patients should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and/or respiratory depression.

The following agents were shown to enhance the metabolisation of diazepam: rifampin, phenytoin, carbamazepine, phenobarbital, and cigarette smoking. This list is not comprehensive and the possibility of interactions between diazepam and any substance known to alter hepatic metabolism should be considered.

In many of the above cases, the clinical significance of the interaction is currently unclear due to broad therapeutic index of diazepam.

2.5.3.4 Dynamic interactions

Combined use of diazepam with other psychotropic agents or centrally depressing agents (e.g. antipsychotics [neuroleptics], anxiolytics/sedatives, antidepressants, hypnotics, narcotic analgesics, anaesthetics, centrally acting muscle-relaxants, antiepileptics, sedative histamines) may potentiate the action of diazepam and result in enhanced sedation, respiratory and/or cardiovascular depression. Therefore patients should be monitored for respiratory depression when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary. In the case of narcotic analgesics, euphoria may be amplified potentially leading to an increase risk of psychic dependence.

2.5.4 Overview of Efficacy

2.5.4.1 Epileptic and febrile convulsions

Epileptic convulsions

Intravenous diazepam is a well established agent in the emergency management of bouts of increased seizure activity in epileptic patients who are on stable regimens of other anti-epileptic drugs, e.g. for the initial control of status epilepticus and severe recurrent convulsive seizures. Rapid penetration of i.v. diazepam into the brain quickly and effectively stops seizure activity in up to 90% of patients, largely independent of the type or aetiology. Large, double-blind clinical study in adults confirmed that i.v. diazepam was as effective as lorazepam or phenobarbital as a first line treatment of overt status epilepticus. [39,40] The authors explained their overall lower success rate (56% for diazepam) compared with figures usually cited in the scientific literature by their more stringent definition of treatment success (cessation of all motor and EEG seizure activity within 20 minutes after treatment start and no relapse during the next 40 minutes). Using a strict methodology, a similar efficacy of i.v. diazepam was also reported in children (65% success rate, median latency to stopping of seizure 5 minutes). [41]

Although i.v. diazepam is the preferred route of administration, available scientific evidence confirms that rectal diazepam is particularly helpful in the treatment of seizures in toddlers, infants, and children. [42] Especially in the seizing paediatric patient, i.v. access is often difficult and cannot readily be obtained; inadvertent administration errors were repeatedly reported to result in important sequelae, e.g. paravenous injection, arterial necrosis, and in very rare cases even limb loss. [43,44]

Compared with the i.v. route, the time to peak plasma levels and thus the onset of action is slightly but not relevantly delayed after rectal administration (see 2.5.2 and Table 1). On the other hand, the rectal route results in a longer duration of action and also decreases the incidence and severity of adverse effects such as respiratory depression and hypotension, which are a significant safety concern with i.v. (bolus) injections.

Seigler (1990) reviewed a total of 18 publications on the use of rectal diazepam for the emergency management of seizures; to this purpose, several different commercially available undiluted parenteral formulations of undiluted injectable diazepam were used. [45] In total, 31 adult patients (range: 18 to 60 years) and 724 children (range: neonates to 16 years) were enrolled in these studies; diazepam was administered rectally using different techniques, but always devices were inserted 4 to 6 cm in the rectum. The initial adult dose ranged from 10 to 30 mg, and the paediatric dose from 0.12 to 1.0 mg/kg. In 13 of these papers, diazepam plasma concentrations were measured and indicative of rapid absorption via the rectal mucosa. Therapeutically relevant concentrations were achieved within 4 to 15 minutes in all studies; peak plasma concentrations and time to peak plasma concentrations were variable and also depended on whether repetitive doses of diazepam were required. In one of the prospective studies included in this review, seizure activity was stopped in 96% of children if treatment with rectal diazepam was instituted within 15 minutes of onset; only in case of prolonged seizures activity for more than 15 minutes, success rate of rectal diazepam decreased to 57% as is known to occur with other routes and compounds. In three of these studies EEG were recorded; these studies confirmed that the efficacy of rectal diazepam was paralleled with EEG-changes as otherwise observed with the i.v. administration of diazepam. [46] Based on its review the author considered rectal diazepam as an excellent alternative to the intravenous route, while effective in ≥ 80% of cases and being safe and convenient to use in emergency situations.

Other investigations not included in the above review and more recent publications corroborate these conclusions. [2,13,47,48,49] In a study in 30 paediatric patients – all < 18 years and suffering from status epilepticus mainly unrelated to epilepsy – clinical results achieved in the pre-hospital treatment with rectal diazepam were essentially similar to those of the i.v. formulation. [13] Seizures subsisted

within 10 minutes after a single dose of 0.16-0.57 mg/kg rectal diazepam in 13/16 children (81%) compared with a 100% success rate in the i.v. group (0.04-0.33 mg/kg); the three non-responders in the group with rectal administration were reported to have serious underlying co-morbidity requiring multiple anticonvulsants and endotracheal intubation in two cases. The longer duration of action reported for rectal diazepam may explain why the recurrence rate before arrival at the emergency department in this group was only half of that in the i.v. group (30% versus 60%).

Rectally applied diazepam (using undiluted injection solutions) in doses from 0.16 mg/kg to 0.6 mg/kg effectively controlled seizures in 5 paediatric patients (11 months to 8 years) with status epilepticus within 1 to 35 minutes. [48] The authors reported that with an initial dose in the higher range (≥ 0.5 mg/kg), seizures ceased more rapidly (in 1 to 3 minutes). With lower doses (applied in stepwise fashion for fear to induce respiratory depression) seizure activity stopped when the total dose approached 0.5 mg/kg.

Available results demonstrate that the composition of the solution used is not important, as long as adequate diluents and/or excipients are used. [49] Rectal administration of an extemporaneous solution prepared by diluting an injectable formulation of diazepam into 50% propylene glycol achieved a high success rate; 84% of a total of 154 episodes of status epilepticus in 103 multiply handicapped patients, both children and adults were successfully treated. More recently, a gel formulation of diazepam for rectal administration having a delayed systemic availability ($t_{max} \approx 90$ min) has been developed and tested in clinical studies for management of seizures in children and adults. Compared with placebo the seizure frequency during a 12-hour observation period was significantly reduced, the time-to-next seizure prolonged, and the percentage of seizure-free patients increased. [50,51,52] Emergency room visits decreased and an improved quality of life, due to reduced family stress, was reported by 58% of families. The prominent side effect of diazepam was somnolence while respiratory depression was not different between groups.

In contrast, one study reported a relatively low success rate. In this study, young patients (age range: 5 to 22 years) with severe epilepsy from a residential centre were enrolled. [2] Response to rectal diazepam was observed in 23/39 (59%) continuous seizure episodes lasting more than 5 min duration. The authors plausibly explained the relatively low efficacy rate by the fact that the collective investigated suffered from particularly severe disease that was known to be difficult to treat. Seizures subsisted within 4 to 12 minutes (median 8 min) after administration and no dependency of efficacy on the seizure type was noticed. No clinically important cardiorespiratory events were identified.

Due to the easy of administration, rectal diazepam lends itself also to administration in the prehospital setting as well as by parents and other caregivers. To guarantee the safety of this approach, a common guideline for home use of rectal diazepam in children was issued in 1995 by the Epilepsy Society of Australia, the Child Neurology Study Group, the Australian Association of Neurologists and the National Epilepsy Association of Australia. [1] Accordingly, home use of rectal diazepam was suggested in a) patients with a pattern of *prolonged seizures* (>10 minutes) who previously responded to i.v. or rectal diazepam; b) in patients who tend to have '*clusters*' of seizures; c) patient who have a history of *spontaneous status epilepticus* and previously responded to diazepam; d) in patients with a history of severe epilepsy who are remote from emergency services at home before transport to hospital.

Treatment of febrile convulsions

Use of a rectal diazepam solution is still recommended in the emergency management of new febrile seizures and represents a valuable and easy-to-use treatment option, especially in children at high risk and/or those living far away from medical care. [53,54] A limited efficacy of rectal diazepam and poor seizure control is only observed in rare cases of long-lasting recurrences.

Prophylaxis of febrile convulsions

The prophylactic use of diazepam during febrile episodes in children who experienced a previous febrile seizure had been favoured for quite some time though this has also been seen with restraint as central side effects of diazepam might interfere with the parents' and clinicians' ability to distinguish benign childhood febrile illness from more serious diseases (e.g. meningitis). Moreover, fear for such side effects was suspected to impair the parents' compliance with the treatment directives. This issue was addressed in a large randomised, double blind trial including 406 children. [55] Short-term results confirmed that diazepam was effective in preventing seizure episodes though 25% to 30% of the children were found to be irritable, lethargic, or ataxic after taking diazepam. A subgroup analysis restricted to children who had seizures while definitely receiving the study drug showed an 82% reduction in the risk of febrile seizures with peroral diazepam compared with placebo.

However, long-term follow-up of children provided strong evidence that the vast majority of febrile seizures do no harm and that prevention of new febrile convulsions is of little long-term benefit, neither with regard to the incidence of subsequent epilepsy nor concerning later neurological, motor, intellectual, cognitive or scholastic ability.

For these reasons, prophylaxis of febrile seizures currently is no longer considered indicated or recommendable.

Dose recommendations

The initial recommended dosage varies by age and is higher in infants (0.5 mg/kg) compared with adults (0.25 mg/kg). Thus, in infants aged 1 to 3 years (10-15 kg) one 5 mg tube of Diazepam Desitin® rectal solution should be used; in older infants (>3 years; >15 kg) one 10 mg tube of Diazepam Desitin® rectal solution should be administered. The dosage in adults is 20 mg diazepam, corresponding to two 10 mg tube of Diazepam Desitin® rectal solution.

The treatment should be administered with the child lying on their side or prone, to guarantee high and rapid pharmacokinetic input and corresponding efficacy. Because of the small volume, the inconvenient procedure to squeeze together the child's buttocks for a few minutes to avoid discharge of the drug is not required.

If no effect is seen after 10 minutes, a second dose may be administered in children or an additional 10 mg tube given in adults.

For elderly or debilitated patients or those with liver or kidney dysfunction it is recommendable to start with a lower dose e.g. 0.25 mg/kg. Conversely, patients on maintenance benzodiazepines may be tolerant and require a larger dose.

Rectally administered diazepam is readily distributed to other (fatty) tissues and the concentrations in the brain and serum fall rapidly. Therefore, appropriate anticonvulsant follow-up treatment is indicated to prevent recurrence.

2.5.4.2 Relief of muscle spasms due to tetanus

Diazepam Desitin® rectal solution is also a valuable alternative in the acute symptomatic treatment of severe spasticity, especially if the intravenous route is not available or undesirable. Doses administered are essentially similar to those used with i.v. administration (normal adult dosage 10 to 20 mg). As with the other indications, Diazepam Desitin® rectal solution does not lend itself to chronic treatment.

Adjunct therapy for the relief of skeletal muscle spasms is an FDA-approved indication of diazepam in both children older than 6 months and adults. As such it may be used primarily in the symptomatic treatment of tetanus, but also to relieve skeletal muscle spasms of various origins, e.g. those associated with a local pathology (reflex spasms due inflammation of the muscles or joints, or secondary to trauma), those caused by upper motor neuron disorders (such as cerebral palsy and paraplegia), or those due to multiple sclerosis and spinal cord lesions. [56,57] In a review article, the effectiveness and

clinical usefulness of diazepam in relieving musculoskeletal spasms of various origins including reflex spasms due to a local pathology (e.g. inflammation of muscles or joints, radiculopathy, osteopathy) has been highly favourably summarised. [56]

Diazepam still is one of the mainstays in the treatment of tetanus. Already in the 70ies, addition of diazepam to a conventional tetanus drug regimen consisting of chlorpromazine, phenobarbital, and paraldehyde was shown to achieve favourable overall effects. In this investigation on 200 consecutive tetanus cases, diazepam led to a statistically significant decrease in the overall mortality in the non-neonate and severe degree tetanus subgroups compared with conventional treatment. [58] Because of the specific nature of the disease, there is lack of data from well-designed, controlled experimental studies in tetanus. Nevertheless, the available evidence strongly suggests that diazepam effectively relieves muscle spasms and rigidity associated with the condition.

For skeletal muscle spasms the usual initial dose reported in the scientific literature is 5 to 10 mg either by the i.m. or i.v. route; therefore the dose of rectal diazepam should be in the same order of magnitude. If necessary, an additional 5 to 10 mg dose may be given after 3 to 4 hours. In severe cases, diazepam is usually administered at relatively high doses of > 20 mg/kg/day via continuous intravenous i.v. infusion; during the stay on the Intensive Care Unit, of several weeks, cumulative diazepam doses of up to 45 grams have been reported. [59] Resulting average plasma concentrations thus were higher than those usually measured during administration in other indications, and amounted to 2.3 ± 0.6 µg/mL for diazepam, 3.3 ± 1.0 µg/mL for desmethyldiazepam, and 0.7 ± 0.5 µg/mL for oxazepam. [60]

2.5.4.3 Use as a sedative in minor surgical and dental procedures

Diazepam and other benzodiazepines have been used for decades as a premedication to provide sedation and to alleviate apprehension, excitement, and anxiety prior to various interventions. This facilitates conduct of the procedure for the physician and improves the patient's comfort; moreover, recall of the procedure by the patient is diminished. Comparative clinical data on the use of rectal diazepam for the symptomatic relief of anxiety and tension in patients undergoing surgical, dental, or diagnostic procedures are scarce. Therefore, reference is taken on results with the i.v. preparation of diazepam for which this indication has been approved by the FDA, both in children older than 1 month and adults.

The usefulness of single-dose premedication with i.v. diazepam and the low incidence of cardio-respiratory side effects have been proven in numerous studies. Based on the results of a placebo-controlled, double-blind study performed in the late 60ies in 800 patients, Steen and Hahl concluded that 10 mg of i.v. diazepam is the dose required in most patients for preoperative sedation. [61] Favourable results were also reported in other early large, double-blind studies in patients scheduled for bronchoscopic or gastrointestinal endoscopic examinations. [62,63] As compared with meperidine or midazolam, i.v. diazepam at doses of 5 to 20 mg was shown to be an effective and safe premedication allowing quick and safe endoscopy; no adverse reactions were observed with either drug. Oral diazepam (0.2 mg/kg) also resulted in adequate sedation in children undergoing various elective surgical procedures though compared with clonidine psychomotor functions were more depressed. [64]

Broader use of i.v. diazepam in this indication has mainly been limited by the relatively important incidence of phlebitis, possibly resulting from the propylene glycol or benzyl alcohol vehicles. An emulsified formulation of i.v. diazepam seems to have solved this problem of tolerability and was recently shown provide the same quality of conscious sedation than i.v. midazolam in 211 patients receiving both upper (oesophagogastroduodenoscopy) and lower endoscopic procedures (colonoscopy). [65] With a mean dose of diazepam of 10.5 mg, there were no significant between group differences in time to adequate sedation, recovery time, requirement for reversal agents, or oxygen needed. Compared with placebo, oral diazepam 10 mg did not affect preoperative anxiety in female

patients undergoing cholecystectomy as assessed by the Hamilton test for anxiety and a visual analogue scale; systolic arterial blood pressure was significantly lower in the diazepam group. [66]

Especially in children, due to its non-invasiveness, diazepam premedication by the rectal route (at doses of 0.1 mg/kg up to 1.0 mg/kg) has also been extensively practised [67,68,69] As can be expected on the basis of the pharmacokinetic data cited above, a rapid onset of action, short duration of action, and a low incidence of adverse reactions were observed; peak plasma levels of diazepam were reached within 30 minutes, with a decrease over the subsequent 2 hours. [70] Rectally administered diazepam (0.7 mg/kg) was effective and safe as a premedication in children undergoing dental extractions. [71] The level of anxiety and sedation was comparable with that after rectal administration of midazolam; only minor adverse effects were observed in both groups. Higher and more reliable diazepam serum levels were achieved in children (11-22.5 kg) prior to minor surgery under general anaesthesia after use of a solution formulation (1 mg/kg) compared with suppositories. [72] Suppositories containing 5 mg diazepam or 60 mg pentobarbital sodium were comparable with regard to their effects on several parameters when used as a premedication in 75 small children (age 3.5 ± 1.1 years) prior to surgery. [68] 19% of children in the diazepam group showed no response to venipuncture, and other 43% were apprehensive, but without hand withdrawal.

Compared with more recent benzodiazepines (midazolam) a somewhat longer recovery period was reported with diazepam. Thus, depending on the expected duration of the intervention Diazepam Desitin® rectal solution may complement the armamentarium at hand of the physician and may be especially useful as a single-dose premedication in children undergoing minor surgical, dental or endoscopic procedures. Rectal administration in children eliminates the stress and trauma due to i.v. or i.m. injection. Compared with the i.v. formulation onset of action only a few minutes delayed whereas duration of action is slightly prolonged.

2.5.4.4 Initial use in anxiety and agitation

Symptomatic relief of anxiety and tension associated with anxiety disorders, transient situational disturbances, and functional or organic disorders is an FDA-approved indication of i.v. diazepam, both in children older than 6 months and adults. In exceptional cases, when the i.v. route is not available, an initial rectal dose of diazepam may be administered.

2.5.5 Overview of Safety

In general, diazepam has a benign safety profile and the majority of reported side effects were of mild to moderate in severity in individual studies. This was also confirmed in a review, which analysed 18 articles involving 755 adult and paediatric patients and receiving a total of 840 doses. [45] The incidence of significant systemic side effects with diazepam is very low.

Elderly or debilitated patients may be particularly susceptible to side effects and therefore, use of lower doses should be considered, also because of age-dependent changes in clearance and half-life.

Case reports of fatalities following use of diazepam have been published; however, the events were associated with unusually high doses and/or concomitant administration of potentially toxic doses of other compounds. [73]

During the last decades, significant clinical evidence has also accumulated on rectal administration of diazepam, mainly with use of the parenteral formulation. Besides transient irritation no relevant local side effects were observed; the spectrum of systemic side effects can reasonably be assumed to be comparable with those reported with other routes of administration (i.v., i.m.).

2.5.5.1 Local side effects to be expected

No specific clinical study addressing the local tolerability of Diazepam Desitin® rectal solution has been performed. However, this is not deemed necessary in view of the fact that the main excipients used (alcohol, propylene glycol) are well-known. Besides transient burning and slight local irritation, no relevant local tolerability problems are expected with intermittent administration of Diazepam Desitin® rectal solution by the rectal route. The extent of rectal irritation after rectal administration of a diazepam solution was assessed in 24 healthy adults using a triple cross-over design. [74] A burning sensation was reported by none of the subjects receiving placebo, and by 3 subjects (12%) receiving a dose of 10 mg; only with the high dose (35 mg) 60% complained of burning for up to 15 minutes after administration. Endoscopic assessment 24 hours later showed mechanical irritation in three subjects and local irritation (caused by diazepam or the vehicle or both) in four subjects. No relevant findings were identified during control endoscopy after 7 days. The rectal tolerance of various vehicles for diazepam microenemas was assessed in a crossover study in 10 subjects. [75] The enema vehicles contained water or water in combination with either propylene glycol and alcohol or glycoferol and alcohol. No significant difference was observed in the vehicle effects and no irritation was encountered.

2.5.5.2 Systemic side effects to be expected

The primary systemic adverse effects are secondary to the pharmacological action of enhanced CNS GABA activity. The spectrum of side effects to be expected with Diazepam Desitin® rectal solution is similar to that known for the i.v. route of administration. However, the slower rise in diazepam serum levels after rectal compared with i.v. administration can be expected to yield a lower incidence and milder intensity of eventual cardiovascular and respiratory side effects (hypotension, respiratory depression).

Furthermore, the rectal solution is generally used only for a short period of time and mainly intermittently. For this reason, adverse effects often associated with chronic diazepam use (tolerance, dependency, withdrawal phenomena) are rare and eventual acute adverse effects are generally rapidly transient and short-lasting.

Nervous system disorders.

The most commonly reported adverse effects relate to the central nervous system and include sedation, drowsiness, somnolence, fatigue, and ataxia. Less frequently, confusion, depression, headache, slurred speech, tremor, and vertigo. Paradoxical reactions of CNS hyperactivity occur rarely and manifest primarily as restlessness, agitation, anxiety, irritability, aggressiveness, rages, hallucinations, delu-

sions, psychoses, nightmares, insomnia, sleep disturbances, and stimulation. Retrograde amnesia was experienced by a 23-year-old patient having taken diazepam (5 mg t.i.d.) for three days because of back spasms; he was diagnosed as being in a fugue-like state with retrograde amnesia and symptoms resolved within 24 hours with amnesia of the event. [76] In several clinical investigations cognitive and memory function was found to be impaired after diazepam intake. [77,78] Acute use of the drug had the most effect on memory, and after discontinuation of the drug, memory function is restored. While diazepam (5 mg) did not interfere with immediate memory it impaired delayed recall of word lists.

Cognitive and psychomotor abilities may be impaired at therapeutic doses. Diazepam slows afferent nerve conduction thereby lengthening reflex motor response at the spinal level and impair driving performance under controlled laboratory tests. [79,80] These effects may have led to the increased risk of hip fracture reported in elderly patients receiving various hypnotic / anxiolytic agents with long elimination half-lives (> 24 hours), including diazepam. [81] There was a good correlation between risk and dose of the drugs in this case-control study in 1021 patients with hip fracture.

Cardiovascular disorders.

Hypotension and bradycardia have been reported, mainly following (too rapid) i.v. injection; in rare cases, severe hypotension and cardiac collapse occurred. With i.v. diazepam, cardiac dysrhythmias (unifocal ventricular premature beats, nodal rhythm, atrial premature beats, bradycardia, and tachycardia) were seen in seven out of 20 (35%) diazepam-treated patients during oral surgery. [82] As mentioned in the introduction of this chapter, there is general agreement that cardiovascular compromise is less frequent and less severe with rectal diazepam. Systolic and diastolic blood pressure were only slightly decreased after rectal diazepam (median decrease of 6.0 mmHg and 8.5 mmHg, respectively). [2]

Respiratory disorders.

Respiratory depression and/or apnoea were mainly described with i.v. administration of diazepam. Precipitating factors influencing the occurrence of the reaction include too fast (bolus) administration, a large total dose, or administration in high risk patients; in addition, vehicle effects on toxicity were also stressed. [83] In 11 out of 122 patient episodes (94 children) presenting to a hospital with seizures, respiratory depression was observed after administration of i.v. diazepam; in 8 cases ventilation was required. [84] In healthy males preoperative treatment with oral diazepam (10 mg) resulted in a significant decrease in both arterial oxygen tension and alveolar-arterial oxygen tension difference. [85] The authors concluded that these effects might become clinically important in patients with impaired cardiorespiratory reserve. Patients at high-risk for developing respiratory depression include those with an underlying pulmonary disease (e.g. chronic bronchitis, chronic airway obstruction or compensated respiratory failure) or those concurrently receiving other drugs with respiratory depressant effect (e.g. narcotics).

As a measure of precaution, lower starting doses of rectal diazepam may be preferred in such patients at high-risk for cardiorespiratory depression. However, in contrast to either oral or i.v. administration, rectal administration did not appear to induce relevant respiratory depression. [2]

Blood and lymphatic system disorders.

Isolated cases of blood dyscrasia (pancytopenia, neutropenia, anaemia) have been reported, in particular with prolonged administration of diazepam. In two cases of diazepam-induced thrombocytopenia, benzodiazepine-dependent antibodies with antiplatelet activity were identified using in vitro techniques. The diagnosis was confirmed by drug challenge in one patient who developed purpura, gingival bleeding and haematuria within 6 hours of diazepam re-exposure. [86]

Eye disorders.

Blurred vision and diplopia were commonly reported by patients taking diazepam. [87] In contrast to earlier reports, no significant increase in intraocular pressure was reported in patients scheduled for routine eye surgery and premedicated with oral diazepam (0.2 mg/kg). [88] Therefore, diazepam Desitin® rectal solution may used in patients with open angle glaucoma who are receiving appropriate therapy; use should still be avoided in acute cases of narrow angle glaucoma.

Musculoskeletal disorders.

Muscle weakness is commonly reported by patients taking diazepam. Two cases of hyponatraemia were reported in 2 patients in whom benzodiazepine intake (lorazepam for 6 months, diazepam for 2 days) was supposed to have contributed to the development of rhabdomyolysis. Both patients recovered with adequate therapy. [89]

Gastrointestinal disorders.

Nausea, vomiting, epigastric pain, constipation, diarrhoea, hiccups, and salivation changes have been observed.

Hepatobiliary disorders.

Cholestatic as well as hepatocellular jaundice have been reported during diazepam use; furthermore a case of hepatic injury during intake of therapeutic doses of diazepam (5 mg t.i.d.) was reported in a 45-year-old male. [90] Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase returned to normal three days after withdrawal. Rechallenge with diazepam again increased liver enzymes within 48 hours; liver biopsy revealed focal necrosis and intracellular cholestasis. Diazepam (and halazepam) in large doses produced a dose-related liver toxicity while other benzodiazepines (e.g. alprazolam) do not.

Skin disorders.

An acute neutrophilic dermatosis (Sweet's syndrome) was diagnosed in a 70-year old male patient after having taken diazepam for 5 days; symmetric bilateral red plaques on the outer aspects of both hands were accompanied by fever and severe arthralgias. [91] Symptoms were not explained by an underlying condition such as infection or an inflammatory, immune, or neoplastic disease. Upon discontinuation of diazepam and corticoid treatment the skin lesions cleared within 10 days; no recurrence was observed during the 10-month follow-up period.

Renal and urinary disorders.

In rare cases, urinary retention has been observed. A case of allergic interstitial nephritis and deterioration of pre-existing chronic renal failure was reported in a 55-yr-old patient who received diazepam for 2 months. [92] The patient was also receiving atenolol, nitroglycerin, diltiazem hydrochloride, and isosorbide dinitrate for hypertension; withdrawal of diazepam led to gradual normalisation of renal function and accompanying signs and symptoms (eosinophilia, itching). Rechallenge was not performed, and therefore it was difficult to definitely ascribe this patient's symptoms solely to diazepam.

A transient decrease in glomerular filtration rate (inulin clearance) and paraaminohippurate clearance was observed in 6 children given 4 mg of i.v. diazepam without measurable change in blood pressure. [93]

Endocrine / metabolic disorders.

Case reports of gynecomastia have been reported in men taking usual or abusive daily doses of diazepam. [94,95] Raised serum estradiol concentrations were measured while hepatic and thyroid function and serum testosterone levels were normal. [96]

Both oral and i.v. diazepam were shown to be potent stimulators of the secretion of growth hormone; tolerance to this effect occurs after administration of therapeutic doses for prolonged periods. [97]

Hypersensitivity reactions, anaphylaxis.

Hypersensitivity reactions including anaphylaxis are very rare; isolated case reports of anaphylactic reactions including rash and urticaria were reported with the use of diazepam. [98,99]

2.5.5.3 Use in special populations

Liver disease:

Since the major site of metabolic breakdown of diazepam by demethylation, hydroxylation, and conjugation is in the liver, metabolism of diazepam is known to be impaired in patients with liver disease, resulting in a prolonged elimination half-life. Reduced clearance in patients with liver cirrhosis leads to higher steady-state plasma levels of diazepam and desmethyldiazepam (nordazepam) compared with controls, resulting in increased clinical sedation. [100,101] Therefore, with chronic use in cirrhotic patients, daily dosage should be reduced by about 50%. With low and single/ intermittent doses of diazepam as to be expected with Diazepam Desitin® rectal solution, the clinical response of patients with liver disease is not expected to differ from that reported for normal subjects. In 23 patients with liver disease, 10 of whom had previous or current clinical evidence of hepatic encephalopathy, no prolonged deterioration in conscious level was noted after administration of 5 mg diazepam. [102]

Renal disease.

In patients with end stage renal insufficiency on maintenance haemodialysis diazepam half-life was markedly reduced compared with healthy controls (mean 37 hr versus 92 hr) and total clearance correspondingly increased. [103] This was mainly due to differences in drug binding and distribution while the clearance of unbound drug remained unchanged; the mean unbound fraction of diazepam in renal failure patients was greatly increased (7.0%) over controls (1.4%), and the volume of distribution reduced. Therefore a dose reduction may be required in patients receiving diazepam on a chronic basis, while no specific dosage adjustment is considered to be necessary in renal insufficiency by other authors, even if the GFR is < 10 mL/min. [104] Nevertheless, it would be prudent to monitor such patients closely when receiving doses > 15 mg/day, as the active metabolites which are excreted by the kidneys might accumulate.

Obese patients.

Due to a prolonged accumulation half-life of diazepam and its metabolite desmethyldiazepam and a resulting larger volume of distribution, it takes more time to achieve effective or optimal drug levels as compared with normal weight individuals. Similarly, therapeutic or adverse effects may persist for longer periods of time in obese patients after discontinuation of repeated dose therapy due to a prolonged elimination half-life. [105]

Elderly patients.

Elderly patients require lower doses and lower plasma levels of diazepam than younger patients to achieve the same degree of CNS depression; both the dose to achieve a specific effect and the resulting plasma level were inversely correlated with age. [106,107]

Usage drug pregnancy.

Benzodiazepines are known to exert differential effects on vestibulo- and visual oculomotoric function [108]: benzodiazepines reduce the velocity and prolong the duration of saccades [109], impair gain of pursuit eye movements [110], decrease gain [111] and shorten the time constant of the vestibulo-ocular reflex [112], whereas others have reported an increase in the time constant [113]. Investigations of saccadic eye movements (peak saccadic velocity) and smooth pursuit eye movements (smooth pursuit gain) have been used to characterise the pharmacodynamic effects of benzodiazepines [114,115,116]; additionally, increased saccadic latency caused by benzodiazepines is known to be a confounding factor in vestibular function testing [117]. Disturbance in various eye movements [118]

and further ocular untoward effects [119] have been seen with benzodiazepines, whereas ocular untoward effects are not uncommon with antiepileptic medications in general [120,121].

Recently, attention has been drawn on the occurrence of neonatal nystagmus in children exposed to drug abuse (opiates and benzodiazepines) in utero [122]. The illicit use of diazepam in utero, particularly in combination with other substances of abuse, is to be considered in the differential diagnosis of neonatal nystagmus.

2.5.6 Benefits and Risk Conclusions

Diazepam as the active ingredient of Diazepam Desitin® rectal solution is among the most frequently prescribed benzodiazepine pharmaceuticals. The present non-sterile formulation is available in pre-filled tubes of 2.5 ml volume and specifically intended for rectal administration. The method of administering Diazepam Desitin® rectal solution is simple, not requiring advanced technical skills; therefore, this route also lends itself to prehospital management or home use.

The high lipid solubility and negligible dissociation of diazepam in solution permit prompt absorption across the rectal mucosa and rapid penetration into the central nervous system. Because of the specific characteristics of the rectal circulation, there is little – if any – first-pass biotransformation in the liver. Pharmacokinetic investigations uniformly report that the rate and extent of absorption of diazepam from a rectally administered solution are high, faster and more reliable than after either oral or intramuscular injection and/or after the administration of rectal suppositories. Additionally, although allowing a very fast and effective pharmacokinetic input, rectally administered diazepam is not associated with the typical overshoot plasma concentrations that otherwise might occur with i.v. (bolus) injections. Maximum concentrations were consistently reached about 10 to 30 minutes after administration, with bioavailability averaging 80 to 100%. Peak serum concentrations are lower and are achieved somewhat slower compared with i.v. administration, but faster and more reliably than by routes other than intravenous.

Therefore, Diazepam Desitin® rectal solution is of benefit in all cases where a rapid onset of action is required and establishing an intravenous line is difficult or undesirable. The formulation is intended for single or intermittent use and does not lend itself to chronic treatment.

Though the majority of clinical data have not been generated in prospective, randomised and blinded clinical trials, substantial evidence has accumulated during the past decades; available data in several hundred adult and paediatric patients have documented the efficacy and safety of this mode of administration.

Administration of diazepam by the rectal route was shown to be effective, safe, and simple to use in the emergency management of severe seizures of various origin, e.g. status epilepticus, acute repetitive convulsive or febrile seizures. The non-invasive mode of administration revealed to be particularly helpful and suitable in infants and children. Cessation of seizure activity was usually observed within a few minutes in a high percentage of patients (in most trials >80%) similar to that reported by intravenous administration. Because of diazepam's short duration of anticonvulsant effect, a long-acting anticonvulsant should be initiated simultaneously.

Rectal administration of diazepam was also shown to be effective and safe as a sedative in minor surgical, endoscopic, and dental procedures or in the initial relief of muscle spasms of various origins (e.g. those caused by tetanus). When the disorder is severe, disabling or subjecting the individual to extreme distress, rectal diazepam may also be indicated in the initial use in anxiety and agitation.

The recommended adult dose of Diazepam Desitin® rectal solution ranges from 0.25 to 0.5 mg/kg. Dosages should be adjusted downward and no more than one half of the usual adult dose should be administered in elderly and debilitated patients. If no effect is seen after 10 minutes, a second dose may be given in children or and additional 10 mg tube administered in adults. The dose can be repeated every 12 hours, if needed. In case of high initial doses or with repeat administration, respiration should be closely monitored.

Rectal administration of diazepam has an excellent record of safety; the incidence of both local and systemic side effects is very low; cardio-respiratory depression is rare with rectal diazepam. The lower incidence of respiratory and cardiovascular depression with the rectal compared with the i.v. route can be attributed to the absence of overshoot plasma concentrations that otherwise might occur with i.v. injections.

It is therefore concluded that the clinical efficacy and safety of Diazepam Desitin® rectal solution in the proposed indications could be adequately and sufficiently established. On this basis, it can be accepted that Diazepam Desitin® rectal solution is an efficacious and safe mode of diazepam treatment. The information given in the Summary of Product Characteristics is in agreement with the currently available scientific evidence and provides appropriate guidance for the safe and efficacious use of the medication.

[redacted] April 2003 – Updated March 2011

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