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(54) **PHARMACEUTICAL COMPOSITIONS
 COMPRISING MIDAZOLAM IN A HIGH
 CONCENTRATION**

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(57) **ABSTRACT**

Compositions of midazolam, a benzodiazapine, in concentrations of 35-100 mg/ml are disclosed for the treatment of anxiety, epilepsy and epileptic seizures, invasive surgical procedures and diagnostic procedures and sedation. These compositions are particularly characterized by a solubilizer such as propylene glycol. Preferably, the compositions are aqueous solutions for intranasal administration.

**PHARMACEUTICAL COMPOSITIONS
COMPRISING MIDAZOLAM IN A HIGH
CONCENTRATION**

FIELD OF THE INVENTION

[0001] The present invention relates to the administration of benzodiazepines such as midazolam. In particular, the invention provides improved midazolam compositions for intranasal administration comprising high concentrations of midazolam.

DISCUSSION OF THE PRIOR ART

[0002] Midazolam is a potent benzodiazepine derivative with sedative, anxiolytic, hypnotic, amnesic, anticonvulsant and muscle relaxant pharmacological properties. Because of the basicity of this molecule, it is possible to prepare salts (e.g., with hydrochloric, maleic and lactic acid) which are soluble in water. From these salts, stable aqueous solutions with a pH of 3.5 can be made for intravenous and intramuscular injections of midazolam (Smith et al., 1981; Gerecke, 1983; Persson et al., 1988). Following administration by injection, midazolam is characterized by a fast onset of action as well as short duration of action, due to its rapid metabolic inactivation by liver enzymes. Midazolam is about twice as potent as the classical benzodiazepine diazepam (Randell and Kytta, 1998).

[0003] For drug administration in general, the oral route is probably the most popular route. However, this mode of administration is not suitable for midazolam, as orally delivered midazolam is extensively degraded by first-pass elimination and has also been found to be a substrate for the intestinal drug efflux transporter (Allonen et al., 1981; Crevoisier et al., 1983; Tolle-Sander et al., 2003). The oral absorption of midazolam is therefore relatively low and variable, with absolute bioavailabilities ranging from just 15 to 27% in children (Payne et al., 1989) and from 31 to 72% in healthy adults (Allonen et al., 1981; Heizmann et al., 1983). Other disadvantages associated with the oral administration of midazolam are the slow onset of action and the observed low peak plasma concentrations. These disadvantages are also observed when midazolam is administered rectally (Saint-Maurice et al., 1986; Malinovsky et al., 1993, 1995).

[0004] Rapid onset of the therapeutic action of midazolam can be achieved by intravenous and intramuscular injection (Taylor et al., 1986; Burstein et al., 1997; Uygur-Bayramicli et al., 2002). However, this mode of administration has a number of obvious disadvantages which make it unattractive. For example, injections are painful and not well accepted by the patients, particularly not by young children.

[0005] In light of the foregoing, intranasal delivery of midazolam is a very attractive alternative mode of administration.

[0006] Intranasal drug administration is painless, results in rapid drug absorption and avoids hepatic first-pass elimination. An additional advantage is the ease of administration, leading to better patient compliance. The mucosa of the nasal cavity is constructed from a highly vascularized tissue covered by a pseudostratified columnar epithelium with

ous regions of the gastrointestinal tract, and the buccal mucosa. In addition, nasal midazolam administration results in pharmacokinetic and pharmacodynamic profiles, which are very similar to those observed after intravenous injections (Walbergh et al., 1991; Björkman et al., 1997; Burstein et al., 1997).

[0007] A number of studies have been reported which demonstrate the beneficial effects of intranasally administered midazolam in patients, both in children and adults. When administered in this way, midazolam appears to have a rapid onset of action (about 10 minutes) and a relatively short duration of action (30 to 60 minutes).

[0008] Nasal midazolam at dosages of 0.2 mg/kg has been shown to have sedative and anxiolytic effects in children undergoing various diagnostic and minor surgical procedures, and none of the children had clinical signs of respiratory depression, bradycardia or other side effects (Wilton et al., 1988; Karl et al., 1992; Davis et al., 1995). Comparable clinical results have also been published for nasal midazolam in dosages of 0.3 and 0.4 mg/kg (Theroux et al., 1993; Malinovsky et al., 1995; Kogan et al., 2002). No additional benefit is found for the midazolam dose of 0.3 mg/kg compared to the lower dose of 0.2 mg/kg (Wilton et al., 1988; Davis et al., 1995).

[0009] Nasal midazolam (0.2 mg/kg) also suppresses acute seizures and improves the EEG background in epileptic children (O'Regan et al., 1996; Lahat et al., 1998, 2000). As stated by O'Regan et al., (1996): "The EEG technicians welcomed the intranasal administration of benzodiazepines. Their time was no longer wasted in waiting for medical staff to achieve satisfactory intravenous access for the drugs. Often there is a difficulty in sitting a butterfly needle or cannula, causing the child to cry, become very restless, or to pull the leads off". Moreover, Lahat et al. (2002) concluded that intranasal midazolam could be provided not only in medical centres but, with appropriate instruction, by the parents of children with febrile seizures at home.

[0010] In adult patients undergoing gastrointestinal endoscopy, intranasal administration of midazolam (0.1 mg/kg) is used for the induction of sedation and the nasal route has been shown to cause fewer side effects than intravenous injection (Uygur-Bayramicli et al., 2002). Nasal midazolam is also effective in the short-time management of seizures in adolescent and adult patients with severe epilepsy (Scheepers et al., 2000). In this clinical study the midazolam dosage used was 5 and 10 mg in patients weighing less than 50 kg and more than 50 kg, respectively. Case reports have also shown the sedative effect of midazolam (0.25 mg/kg) in an adult patient with a seizure disorder (Cheng, 1993) and the seizure-terminating activity of nasal midazolam (dose of 4 mg) in an adult epileptic woman (Kendall et al., 1997).

[0011] While the above discussed studies have demonstrated the efficacy of nasally administered midazolam, it should be noted that in all clinical studies mentioned above the commercially available injection solutions, containing midazolam at concentrations of 5 mg/ml (Dormicum®, Hoffmann-La Roche, Switzerland), were used. The use of solutions with this concentration of midazolam requires very large volumes of liquid to be applied intranasally, ranging from 1 ml in children to even 4-5 ml in adults.

drops out of the nose and/or will be swallowed, resulting, at best, in part of the dose being administered orally rather than nasally. This oral midazolam absorption is clearly shown by Burstein et al. (1997). As discussed above, the orally administered midazolam will have a significantly reduced therapeutic effect compared to the intranasally administered midazolam.

[0013] The nasal administration of such large volumes of solution also accounts for a number of unpleasant side-effects sometimes experienced by patients, including lacrimation, burning sensations, irritation in the nose and throat, and general discomfort (Lugo et al., 1993; Burstein et al., 1997; Kogan 2002). In addition, treatment failure can occur due to the inadequate technique of delivering unphysiologically large volumes of the midazolam solution (Scheepers et al., 2000).

[0014] A further problem is clearly the loss of a large proportion of the composition and of the midazolam, which leads to inconsistent and unpredictable amounts of midazolam being absorbed.

[0015] It is therefore clear that the use of commercially available midazolam injection solutions for intranasal midazolam administration is inefficient and unpleasant for the patients, due to the necessary large volumes applied. This can lead to reduced nasal bioavailability and ineffective plasma peak concentrations of midazolam and therefore to an insufficient therapeutic efficacy.

[0016] For efficient and comfortable nasal drug delivery, volumes of about 200 μ l (100 μ l into each nostril) are normally the maximum that should be administered to a patient. This implies that there is an urgent need for the availability of nasal formulations with highly increased midazolam concentrations in comparison with the midazolam injection solutions.

[0017] A few nasal midazolam formulations have been developed which seek to reduce the total volume of liquid to be delivered intranasally to the patients. These formulations are described in detail in Table 1 below.

TABLE 1

Nasal Midazolam Formulations		
Reference	Composition	pH
Lui et al. (1991)	Midazolam HCl 11.1 mg/ml Methocel 1.5% (w/v) Water	about 4
Lofthsson et al. (2001)	Midazolam base 17 mg/ml SBE β CD 14% (w/v) HPMC 0.10% (w/v) Benzalkonium chloride 0.02% (w/v) EDTA 0.1% (w/v) Phosphoric acid 0.43% (v/v) Water	4.3
Knoester et al. (2002a)	Midazolam HCl 30.9 mg/ml Benzyl alcohol 1% (v/v) = 10.46 mg/ml Propylene glycol 25% (v/v) = 259 mg/ml Water	4

HPMC, hydroxypropyl methylcellulose 4000
SBE β CD, sulfobutylether- β -cyclodextrin sodium salt (Captisol®)

(11.1 mg/ml) and 1.5% methocel as a viscosity-enhancing agent. It is prepared by freeze-drying the commercially available midazolam injection solution. The dried product is dissolved in water and mixed with the appropriate volume of a 7.5% methocel aqueous solution.

[0019] The formulation has been tested for nasal midazolam absorption in dogs, and not in human subjects. However, nasal administration of a total volume of 200 μ l of this formulation will not achieve therapeutically effective midazolam plasma levels in humans, because the midazolam concentration in this formulation is far too low.

[0020] The nasal formulation used by Loftsson et al. (2001) comprises midazolam hydrochloride (17 mg/ml) with 14% sulfobutylether- β -cyclodextrin sodium salt (SBE β CD; Captisol®) as solubilizer in an acidic solution at pH 4.3. The presence of 0.1% hydroxypropyl methylcellulose (HPMC) has an additional solubilizing effect. This formulation also contains 0.02% benzalkonium chloride and 0.1% EDTA as preservatives.

[0021] Acute intranasal administration of this midazolam formulation in healthy volunteers (100-160 μ l into each nostril) is associated with mild to moderate transient irritation of the nasal mucosa (Gudmundsdottir et al., 2001).

[0022] A further disadvantage associated with this formulation is that the preservative mixture of 0.02% benzalkonium chloride/0.1% EDTA inhibits the ciliary movement in vitro and is classified as ciliostatic (Merkus et al., 2001). Also the use of the high Captisol® concentration (14%) required to solubilize midazolam will also lead to a strong ciliostatic effect.

[0023] It is known that ciliary beating is the major factor in normal functioning of the nasal mucociliary clearance, which is a very important defence mechanism of the respiratory tract (Martin et al., 1998). Nasal administration of the midazolam formulation of Loftsson et al. (2001) can therefore be expected to disturb the mucociliary clearance of the patients. More importantly, the midazolam concentration of this nasal formulation is too low to provide adequate therapeutic efficacy of the drug.

[0024] The intranasal midazolam formulation used by Knoester et al. (2002a, 2002) and Tenk et al. (2003) consists of midazolam hydrochloride (30.9 mg/ml) in a mixture of 25% (v/v) propylene glycol and water (pH 4). It also contains 1% (v/v) benzyl alcohol as a preservative. A dose of 5 mg midazolam base is delivered by two sprays of 90 μ l and, for a dose of 10 mg midazolam base, 4 sprays of 90 μ l are needed (providing a total dose of 360 μ l).

[0025] The use of this formulation for intranasal midazolam administration in healthy volunteers and in epilepsy patients, providing a dose of 5 mg or 10 mg (90-180 μ l in each nostril), causes nasal irritation, lacrimation and irritation of the throat in almost all subjects, as well as a bitter taste (Knoester et al., 2002; Tenk et al., 2003). In vitro experiments with ciliated tissue, this midazolam formulation has been shown to be ciliostatic, probably due, in particular, to the presence of 25% propylene glycol and 1% benzyl alcohol (Merkus et al., 2001). It is evident from these studies that the volume of the formulation used to administer a dose

adverse side effects. These adverse effects could prohibit the use of this formulation in clinical practice.

SUMMARY OF THE INVENTION

[0026] In light of the foregoing, it is clear that there is the need for a midazolam formulation which is specifically formulated for intranasal administration, in order to overcome all of the various disadvantages associated with the known formulations which are administered intranasally. It is therefore an aim of the present invention to provide a formulation with a high enough midazolam concentration to allow adequate doses of midazolam to be efficiently and comfortably administered via the intranasal route in a small volume. The formulation should also cause as little irritation as possible and have as high a bioavailability as possible. Finally, the formulation should have a similar or reduced ciliostatic effect in *in vitro* experiments, compared to the known nasal formulations.

[0027] These and other objects of the invention are achieved by providing a pharmaceutical composition which comprises a solution of high concentration midazolam and a solubilizer. The composition is preferably provided in the form of an aqueous solution and preferably administered intranasally. Such composition can be administered to patients in the treatment of anxiety, epilepsy and epileptic seizures, invasive surgical procedures and diagnostic procedures and sedation.

DETAILED DESCRIPTION OF THE INVENTION

[0028] According to a first aspect of the present invention, a pharmaceutical composition is provided, wherein the composition is a solution comprising midazolam in a concentration of at least 35 mg/ml (based on the free base form of midazolam), and a solubilizer. The composition may contain midazolam either in the form of its free base or a pharmaceutically acceptable salt thereof.

[0029] The compositions according to the present invention are preferably suitable for intranasal administration.

[0030] In one embodiment of the invention, the concentration of midazolam is at least 40 mg/ml, or at least 50 mg/ml. The midazolam concentration may also be less than 100 mg/ml, less than 75 mg/ml or less than 60 mg/ml. In a preferred embodiment, the midazolam concentration is 35-75 mg/ml.

[0031] In a particularly preferred embodiment of the present invention, the composition is an aqueous solution. The aqueous solutions of the present invention containing high midazolam concentrations are facilitated by the inclusion in the solution of a solubilizer. Particularly effective solubilizers include propylene glycol, glycerol, polyethylene glycol, povidone and ethanol, or combinations thereof. The inclusion of solubilizers not only enables the formation of an aqueous midazolam solution, but also allows that solution to have a high midazolam concentration. The preferred solubilizers for inclusion in the compositions of the present invention are discussed in greater detail below.

[0032] The prior art does not disclose nasal midazolam formulations having such high midazolam concentrations.

tions of up to around 30 mg/ml was the maximum possible (see Table 1). However, this is not true, especially when using propylene glycol alone as the solubilizer or propylene glycol in combination with glycerol and optionally one or more of polyethylene glycol, povidone, and ethanol; and water. It was also considered in the prior art that the formulations for nasal administration should have a pH of no less than about 4, as the intranasal administration of a formulation with a lower pH was thought to be too uncomfortable, due to irritation. These prejudices have led the skilled person to administer large volumes intranasally, leading to the above discussed problems.

[0033] Contrary to the common opinion of the skilled person, the nasal administration of formulations having a pH lower than 4 is not unacceptable to patients. More importantly, the lower pH allows greater amounts of midazolam to be dissolved, allowing composition with higher concentrations of midazolam to be prepared which, in turn, enables smaller volumes of formulation to be administered.

[0034] The high midazolam concentration has a number of surprising advantages. Firstly, as discussed above, it means that smaller volumes of the solution can be administered in order to achieve a desired therapeutic effect. This reduces the waste due to varying amounts of the composition being swallowed or dropping out of the nose, so that more of the administered midazolam is properly absorbed and has the desired therapeutic effect. This also reduces the unpleasant taste and irritation which accompanies swallowing of the nasal composition. It also increases the dose consistency and predictability. This, in turn, enables one to achieve a specific therapeutic effect, as the plasma levels achieved following intranasal administration will be predictable and controllable. As discussed below, different midazolam plasma levels result in different therapeutic effects on the patient. The midazolam compositions for intranasal administration disclosed in the prior art do not result in consistent or predictable plasma levels and so do not permit accurate dosing to achieve a specific therapeutic effect.

[0035] The high midazolam concentration also means that some therapeutic effects which were previously difficult or impossible to achieve using known midazolam compositions can now be reliably achieved. If one can administer just 50-100 μ l per nostril instead of 2, 4 or even 10 times that volume per nostril, this will clearly be beneficial, especially if the patient is nervous or is a crying child or the like. Therefore, in one embodiment of the invention, the composition provides a therapeutically effective dose of midazolam in a total volume of up to about 200 μ l. Preferably, the composition provides a therapeutically effective dose of midazolam in a volume of up to about 100 μ l, it being possible to administer this dose to each nostril.

[0036] Another benefit associated with administering a smaller volume of the composition intranasally is that it results in a smaller area of deposition within the nose. This localised administration within the nose means that any transient irritation will also be localised and limited to a small area within the nose and throat. This, once again, reduces the discomfort experienced by the patient.

[0037] Additionally, the high midazolam concentration has also been demonstrated to enhance diffusion of the

lower midazolam concentrations. This not only means a faster onset of the therapeutic effect, but also a reduction in the time for which the active agent is in contact with the nasal epithelium. Again, this will reduce the patient's discomfort, as the midazolam itself is an irritant. Also, less of the midazolam formulation will reach the throat and so there is less chance for irritation by the formulation ingredients and for experiencing the bitter taste of midazolam.

[0038] In one embodiment of the invention, the midazolam included in the composition is a salt of midazolam, such as midazolam hydrochloride, midazolam maleate or midazolam lactate. Preferably, the composition comprises midazolam hydrochloride.

[0039] In a preferred embodiment of the invention, the solubilizer comprises propylene glycol. Propylene glycol is a good solubilizer for midazolam including salts thereof, e.g. HCl, especially when the midazolam is to be formulated as an aqueous solution. In addition to the propylene glycol, the solubilizer may further comprise one or more of the following: glycerol, polyethylene glycol, povidone, and ethanol. Water is included in the formulation of the preferred solutions.

[0040] In an alternative embodiment of the invention, the solubilizer comprises glycerol, another good solubilizer for midazolam when an aqueous solution is to be formed. In addition to the glycerol, the solubilizer may further comprise one or more of the following: propylene glycol, polyethylene glycol, povidone, and ethanol. Water is included in the formulation of the preferred solutions.

[0041] In a particularly preferred embodiment of the invention, the composition is a solution of midazolam comprising 90-10%, 80-20%, 70-30%, 60-40% or 40-50% (v/v) solubilizer, preferably propylene glycol. The composition preferably also comprises 10-90%, 20-80%, 30-70%, 40-60% or 50-60% (v/v) water. Furthermore, the composition preferably comprises 40-75 mg/ml midazolam. A composition comprising 40-50% (v/v) propylene glycol and 50-60% (v/v) water is considered as being particularly advantageous.

[0042] In one embodiment of the invention, the composition comprises a combination of propylene glycol and glycerol. Glycerol has a sweet taste and, in addition to acting as an excellent solubilizer, it also serves to mask the taste of the midazolam, should some of the solution go down the back of the throat of the patient.

[0043] Propylene glycol and glycerol have further advantages. Compositions comprising solubilizers containing propylene glycol (>15% v/v) and/or glycerol (>20% v/v) do not need to include a preservative, because it is known from the literature that these concentrations of glycerol and of propylene glycol act as antimicrobial preservatives (Handbook of Pharmaceutical Excipients, Third Edition, The Pharmaceutical Press, London 2000).

[0044] Propylene glycol, glycerol, polyethylene glycol and povidone are also attractive solubilizers for use in a nasal solution because they do not have a strong adverse effect on ciliary movement. In *in vitro* experiments, according to a previously published method (Merkus et al, 2001), the effect of four different solubilizers [25% propylene

ciliary beat frequency (CBF) of ciliated tissue taken from chicken embryo tracheal tissue was measured.

[0045] All four compounds showed a decrease in CBF after 15 minutes. However, after rinsing with Locke-Ringer solution, the effects on CBF appeared to be completely reversed within 20 minutes.

[0046] The solubilizers used in the compositions of the present invention should cause as little irritation as possible when administered *in vivo*, and preferably no irritation at all. While transient and mild irritation can be tolerated by patients, this should be kept to a minimum in order to avoid unnecessary discomfort.

[0047] The preferred solubilizers used in the present invention and discussed above will not cause unnecessary irritation upon intranasal administration.

[0048] Despite the reduction in the amount of swallowed composition achieved by using the compositions of the present invention, it is nevertheless possible that a very small part of the midazolam dose will reach the throat, which may lead to a bitter taste. Therefore, in another embodiment of the invention, one or more sweeteners are included in the composition, to mask the bitter taste of midazolam. According to this embodiment, the formulation may comprise midazolam in a concentration of at least 35 mg/ml, a solubilizer and a sweetener.

[0049] Suitable sweeteners for inclusion in the compositions of the present invention include saccharin and saccharin alkali salts (which may be included in an amount of about 0.1-5% w/v), aspartame (which may be included in an amount of about 0.1-5% w/v), acesulfame K and cyclamate.

[0050] Further additional components which may be included in the compositions of the present invention include flavouring agents, preservatives, buffers, stabilising agents and pH adjusting agents, known from the pharmaceutical literature (Martindale 33rd edition, The Pharmaceutical Press, London 2002). In a preferred embodiment, the composition is free from any buffers.

[0051] Suitable flavouring agents include vanilla (vanillin), mint, raspberry, orange, lemon, grapefruit, caramel, cherry flavours and combinations of these.

[0052] Suitable stabilizing agents include cyclodextrins such as beta-cyclodextrin (which may be included in an amount of about 1%) and derivatives of beta-cyclodextrin (which may be included in an amount of about 1-4%).

[0053] In an alternative embodiment, the compositions according to the present invention are free from any preservatives and/or stabilising agents. In another embodiment, the composition is free from benzyl alcohol.

[0054] In a yet another embodiment of the invention, the compositions further comprise a viscosity enhancing agent. Viscosity enhancing agents are well known to the person skilled in the art from the pharmaceutical literature and will include agents such as cellulose derivatives. Enhancing the viscosity of the solution can enhance the delivery of the midazolam. Viscosity enhancing agents such as cellulose derivatives may also serve to increase the stability of the solutions.

[0055] The enhanced absorption of midazolam using the compositions according to the present invention means that

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