39e CONGRÈS ANNUEL DE L'ADARPEF
25 & 26 MARS 2022
MONTPELLIER
Le Corum

Quelle place pour des formulations pédiatriques ?

Marco Caruselli
Service d'Anesthésie Réanimation pédiatrique
Hôpital d'enfants La Timone
Marseille

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Liens d'intérêt

- Pas de lien d'intérêt en dehors de ce symposium*

* Cette présentation a été établie en toute indépendance par son auteur et n'engage pas la responsabilité de Nordic Pharma.

La prémédication est-elle utile?

Research

JAMA. 2015;313(9):916-925. doi:10.1001/jama.2015.1108

Original Investigation

Effect of Sedative Premedication on Patient Experience After General Anesthesia

A Randomized Clinical Trial

Axel Maurice-Szamburski, MD; Pascal Auquier, MD, PhD; Véronique Viarre-Oreal, PhD; Philippe Cuvillon, MD, PhD; Michel Carles, MD, PhD; Jacques Ripart, MD, PhD; Stéphane Honore, MD; Thibaut Triglia, MD; Anderson Loundou, PhD; Marc Leone, MD, PhD; Nicolas Bruder, MD, PhD; for the PremedX Study Investigators

Secondary Outcomes of the PremedX Study

	Lorazepam (n = 330)	No Premedication (n = 319)	Placebo (n = 322)	*P* Value for Lorazepam vs No Premedication	χ^2	*P* Value for Lorazepam vs Placebo
Operating Room Arrival						
Visual analog scale score, mean (95% CI)						
Quality of conditioning	76 (74 to 78)	74 (71 to 76)	73 (70 to 75)	.26		.09
Well-being	67 (64 to 69)	64 (61 to 67)	62 (59 to 65)	.38		.06
Anxiety	35 (32 to 38)	38 (35 to 41)	44 (40 to 47)	.41		.001
Postoperative Day 1 Outcomes						
Amnesia, No. (%)	79 (24)	18 (6)	18 (6)	<.001		<.001
Change in visual analog scale score, mean (95% CI)[c]						
Pain	−8.0 (−11.8 to 4.3)	−6.6 (−10.7 to 2.6)	−7.8 (−11.7 to 3.9)	.88		.99
Quality of sleep	6.4 (2.5 to 10.3)	18.1 (13.9 to 22.3)	17.8 (13.6 to 22.0)	<.001		.001
Well-being	3.9 (0.5 to 7.3)	5.8 (2.7 to 8.9)	4.1 (0.9 to 7.4)	.72		.99

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Pratiques en pédiatrie



ANNALES FRANÇAISES D'ANESTHÉSIE ET DE RÉANIMATION

Anesthésie générale chez l'enfant : quid des pratiques en 2010 ?

05/09/12

Doi : 10.1016/j.annfar.2012.06.004

I. Constant *, N. Louvet, M.-L. Guye, N. Sabourdin

Hôpital Armand-Trousseau, groupe hospitalier HUEP, UPMC, AP–HP, 26, avenue Arnold-Netter, 75012 Pari
France

1150 questionnaires distribués à des MARP, 1025 analysés.
72 % des MARP utilisaient toujours la prémédication

Pourquoi le midazolam?

- Benzodiazépine à court délai d'action
- Médicament sédatif, anxiolytique, amnésique
- Particulièrement adapté à la prémédication en anesthésie

- Défaut principal: gout amère, désagréable pour les enfants

According to (WHO, 2011) and European Medicine Agency (2006) requirements for children's appropriate preparations, oral solutions are suitable for children.

Five guides (Mace et al., 2004; National Institute for Health Care Excellence, 2010, 2016; Editorial Board of Chinese Journal of Pediatrics, 2015; Chinese Medical Association Anesthesia Branch, 2017a) and three expert consensuses (Chinese Medical Association Pediatrics Branch Emergency Study Group, 2014; Chinese Medical Association Anesthesia Branch, 2017b,c) recommend midazolam for children to calm, hypnotize, and counter anxiety. The NICE guidelines recommend oral administration of midazolam for sedation before painful examination in children (National Institute for Health Care Excellence, 2010). Midazolam is included in the WHO, UK, and Indian children's formulas (World Health Organization Regional Office for South-East Asia New Delhi, 2011; Committee P F., 2017; WHO Expert Committee on the Selection Use of Essential Medicines, 2017). The UK Formulary recommends

Que se passe-t-il après administration de midazolam?

The Oral Bioavailability and Metabolism of Midazolam in Stable Critically Ill Children: A Pharmacokinetic Microtracing Study

Bianca D. van Groen[1], Elke H. J. Krekels[2], Miriam G. Mooij[3], Esther van Duijn[4], Wouter H. J. Vaes[4], Albert D. Windhorst[5], Joost van Rosmalen[6], Stan J. F. Hartman[7], N. Harry Hendrikse[5], Birgit C. P. Koch[8], Karel Allegaert[8,9], Dick Tibboel[1], Catherijne A. J. Knibbe[2,10] and Saskia N. de Wildt[1,7,*]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 109 NUMBER 1 | January 2021

- Le midazolam a une absorption intestinale et hépatique (hydroxylation par le cytochrome P450 surtout CYP3A4/5, le CYP3A7 se réduisant rapidement après la naissance.
- La fraction qui rejoint le système circulatoire s'appelle biodisponibilité orale (oral bioavailability).
- Etude multicentrique 46 enfants (nouveau-né – 6 ans), réanimation, midazolam IV continu, « microtraceur » (dose 1/100 de la dose normale) per OS. Prises de sang à 0,5/1/2/4/6/12/24 h.

CONCLUSIONS

- La clearance est très dépendante du poids corporel.
- Prématuré 26-31 semaines/nouveau né âgés de 3-13 j vs l'enfant > 1 an
  - clearance du midazolam est faible (0,16 L/kg/h vs 3 L/kg/h)
  - biodisponibilité orale plus élevée (49-92 % vs 21 %).
- Activité intestinale et hépatique réduite chez les petits < 1 an

Dilution de la préparation IV avec d'autres solutions plus palatables: les expériences

Pediatric Anesthesia

Effect of drinks that are added as flavoring in oral midazolam premedication on sedation success

Correction(s) for this article

BERRIN ISIK MD, ÖZGÜL BAYGIN DDS, HALUK BODUR PhD

First published: 18 March 2008 | https://doi.org/10.1111/j.1460-9592.2008.02462.x | Citations: 17

Methods: In the laboratory; the pH values of 2.5 ml midazolam (15 mg·3 ml^{-1}) and the mixtures of Pepsi Cola®, 10% sodium citrate, fresh pomegranate juice, and fresh grapefruit juice in equal volumes were measured. Seventy-five patients between 2 and 8 years of age who were assessed to have anxiety with the Frankl Behavior Scale and

Anaesthesia 2018 doi:10.1111/anae.14318

Original Article

A novel, palatable paediatric oral formulation of midazolam: pharmacokinetics, tolerability, efficacy and safety

S. Salman,[1] E. K. Y. Tang,[2] L. C. Cheung,[3,4,5] M. N. Nguyen,[2] D. Sommerfield,[6] L. Slevin,[7] L. Y. Lim[8] and B. S. von Ungern Sternberg[6,9]

	All dosed children (tolerability and safety analysis)	
	CDS formulation n = 76	i.v. formulation n = 74
Age; years	7.4 (3.1)	7.5 (3.6)
Sex; male	36 (47%)	37 (50%)
Height; cm	125 (19)[a]	124 (22)[a]
Weight; kg	29 (14)	30 (17)

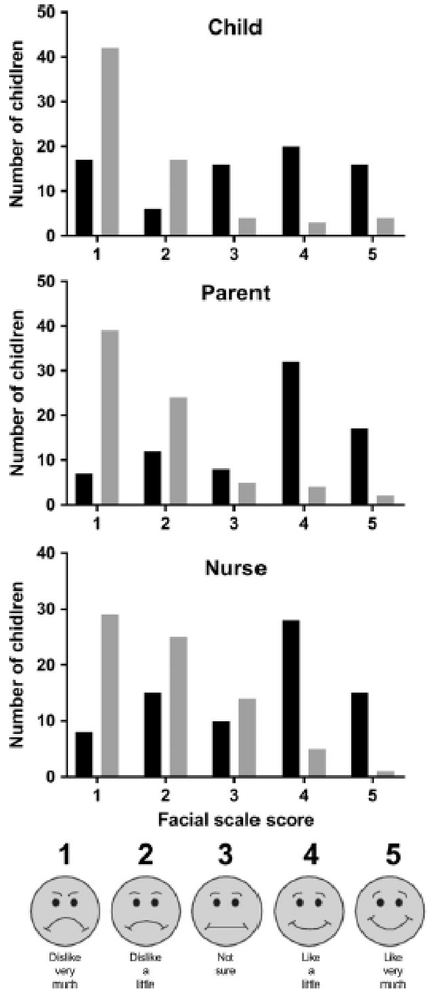


Figure 1 Histogram of patient, parent and nurse scoring of tolerability for the chocolate delivery system (CDS) tablet (■) and i.v. solution (▩) with the 5-point facial hedonic scale used for assessments.

Midazolam Premedication in Children: A Comparison of Two Oral Dosage Formulations on Sedation Score and Plasma Midazolam Levels

Keith K. Brosius, MD, and Carolyn F. Bannister, MD

Department of Anesthesiology, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia

Table 1. Demographic Data

Study group	Age (yr)	Sex (M/F)	Weight (kg)	IV fluids (mL/kg)
IV in Syrpalta® (n = 25)	5.3 ± 1.9	14/11	20.0 ± 6.0	17.8 ± 3.4
Commercial (n = 25)	5.1 ± 1.9	13/12	19.1 ± 5.9	18.2 ± 3.8

Values are mean ± SD where applicable.

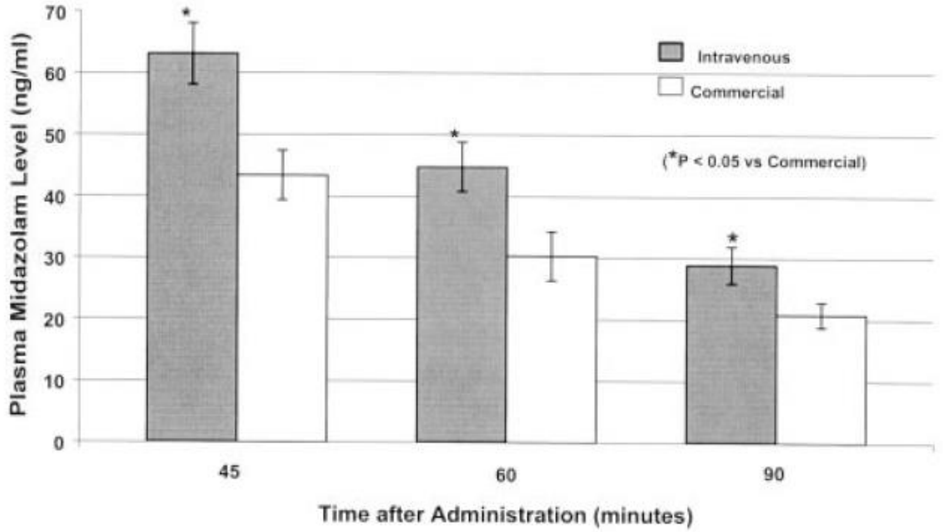


Figure 1. Comparison of plasma midazolam levels at 45, 60, and 90 min after administration between the IV/Syrpalta® mixture and commercial Versed® Syrup. Data are expressed as group mean ± SEM; *$P < 0.05$ between groups.

frontiers in Pharmacology
SYSTEMATIC REVIEW
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Efficacy and Safety of Midazolam Oral Solution for Sedative Hypnosis and Anti-anxiety in Children: A Systematic Review and Meta-Analysis

Xiao Cheng [1,2,3,4†], Zhe Chen [1,2,3†], Lingli Zhang [1,2,3], Peipei Xu [1,2,3], Fang Qin [1,2,3,4], Xuefeng Jiao [1,2,3], Yiyi Wang [1,2,3], Mao Lin [1,2,3,4], Linan Zeng [1,2,3], Liang Huang [1,2,3,5] and Dan Yu [1,2,3,6]*

TABLE 1 | Incidence of adverse reactions to midazolam oral solution.

ADR type	No. of studies included	No. of ADR cases	No. of patients	ADR incidence	PI [95% CI]	Heterogeneity	
						I^2 (%)	*P*
MENTAL SYSTEM							
Prolonged sedation	2	60	96	0.62	0.28 [0.00, 0.97]	94	<0.01
Dysphoria	3	34	157	0.22	0.25 [0.04, 0.73]	94	0.30
Agitation	3	20	126	0.16	0.16 [0.10, 0.23]	0	0.85
Abnormal behavior	2	16	125	0.13	0.15 [0.01, 0.75]	95	<0.01
Euphoria	2	11	147	0.07	0.07 [0.01, 0.42]	88	<0.01
Lethargy or disturbed sleep	2	5	58	0.09	0.09 [0.04, 0.19]	0	0.7
Irritability	2	8	126	0.06	0.07 [0.01, 0.50]	89	<0.01
Inner conflict	2	8	158	0.05	0.05 [0.03, 0.10]	0	0.65
Aggressivity	1	2	97	0.02	0.03 [0.00, 0.20]	–	–
Mood swing	1	1	97	0.01	0.01 [0.00, 0.07]	–	–
Headache	1	1	80	0.01	0.02 [0.01, 0.08]	–	–
DIGESTIVE SYSTEM							
Hiccup	3	6	90	0.07	0.07 [0.03, 0.15]	0	0.61
Nausea and vomiting	13	9	547	0.02	0.03 [0.02, 0.05]	0	0.87
RESPIRATORY SYSTEM							
Laryngospasm	1	1	30	0.03	0.03 [0.00, 0.20]	–	–
Need assisted breathing	1	1	142	0.01	0.01 [0.00, 0.05]	–	–
Other	7	6	324	0.02	0.03 [0.01, 0.10]	56	0.04

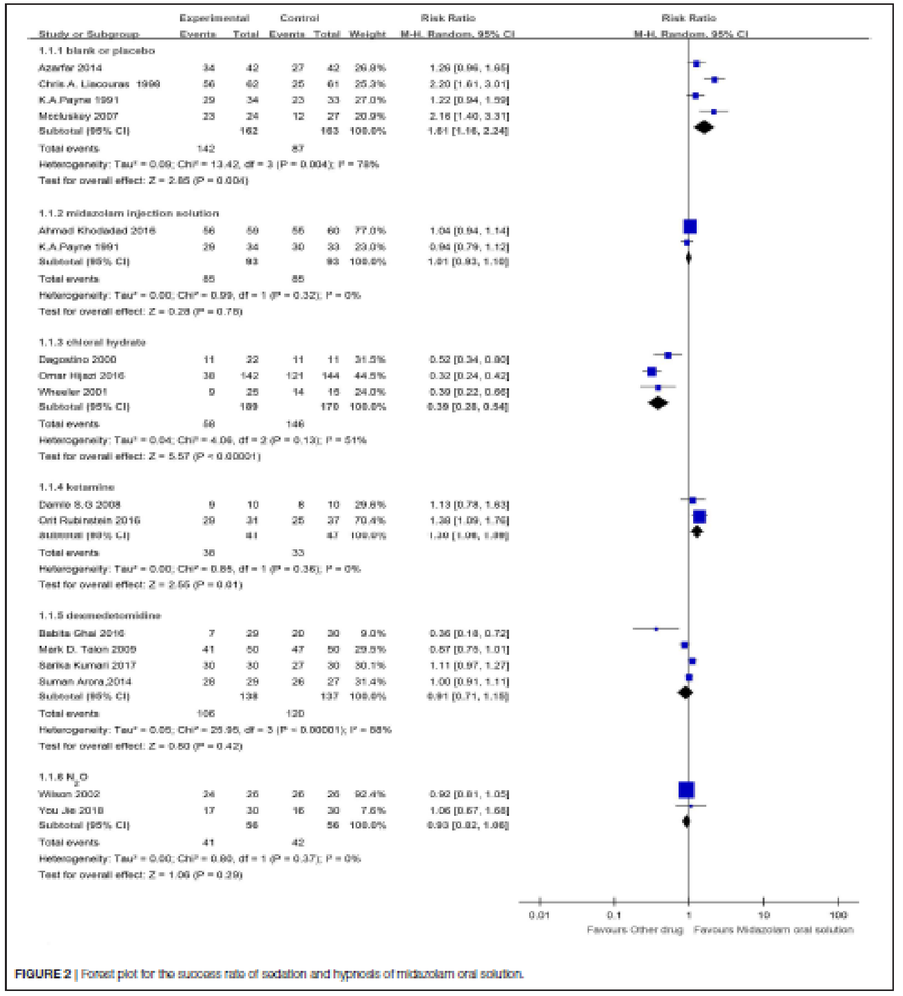


FIGURE 2 | Forest plot for the success rate of sedation and hypnosis of midazolam oral solution.

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ELSEVIER
International Journal of Pharmaceutics
Volume 379, Issue 2, 11 September 2009, Pages 244-250

Development and formulation of a 0.2% oral solution of midazolam containing γ-cyclodextrin

Frédéric Marçon [a], David Mathiron [b], Serge Pilard [b], Anne-Sophie Lemaire-Hurtel [c], Jean-Marc Dubaele [a], Florence Djedaini-Pilard [d]

In absence of dedicated children formulation, intravenous formulations of midazolam, which exhibit strong bitterness, are occasionally used for oral or sublingual administration. In order to improve the quality and the acceptance by children of a midazolam anesthesia premedication, a new 0.2% (w/v) aqueous solution for oral administration has been prepared. The final formulation was obtained by the adjunction of a sweetener (sucralose), an aroma (orange aroma) and γ-cyclodextrin to a citric acid solution of midazolam. The γ-cyclodextrin forms an inclusion complex with the hydrophobic midazolam as evidenced using nuclear magnetic resonance spectroscopy (stoichiometry 1:1, $K = 283\ M^{-1}$). A sterile filtration method was selected for the formulation microbial preservation using liquid chromatography coupled to high resolution mass spectrometry (LC–HRMS). Finally, a routine high performance liquid chromatography (HPLC) method is proposed for the quantitative determination of global midazolam amount in the pharmaceutical preparation.

La dilution du midazolam dans des solutés non conformes peut donner une altération du pH, de la solubilité, de la biodisponibilité et de la pharmacocinétique ce qui peut donner des réponses imprévisibles. Isik B et al. Paediatr Anaesth 2008

European Journal of Pharmaceutical Sciences 114 (2018) 46–54

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journal homepage: www.elsevier.com/locate/ejps

Population pharmacokinetic evaluation of ADV6209, an innovative oral solution of midazolam containing cyclodextrin

Frédéric Marçon[a,f,*], Catherine Guittet[b], Maria A. Manso[b], Ingrid Burton[c], Luc-André Granier[b], Philippe Jacqmin[d], Hervé Dupont[e,g]

Table 1
Summary statistics of subject demographics (NA: Not applicable).

Age group	Phase 1 study	Phase 2 study		
	Adult set	Adolescent set	Young children set	
	Adults ≥ 18 years	Adolescents [12–18 years]	Children [2–12 years]	Infants [6–24 months]
Sex				
Male (n)	6	6	10	5
Female (n)	6	6	7	3
Age (years)				
Mean	43.9	14.4	6.6	1.33
Median (range)	46 (24–56)	13.8 (12–17.5)	6.0 (3.1–11.7)	1.54 (0.5–1.92)
Body weight (kg)				
Mean	62.9	49.0	22.9	11.2
Median (range)	60.5 (49.0–86.0)	47.3 (27.0–82.2)	21.0 (14.0–44.0)	11.5 (7.6–15.0)
Time of anaes-thesia (h)				
Mean	NA	1.22	0.96	0.61
Median (range)	NA	0.67 (0.52–1.92)	0.62 (0.47–3.23)	0.58 (0.50–0.87)

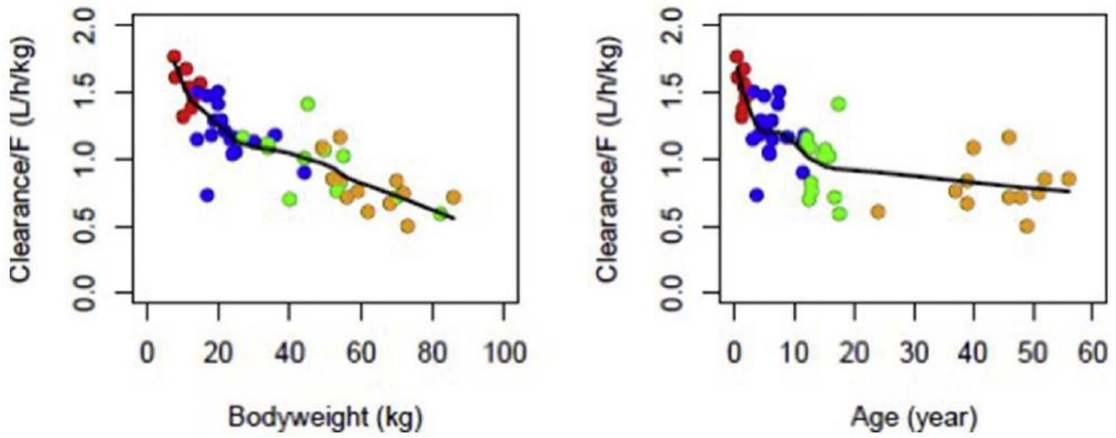


Fig. 4. Midazolam clearance as a function of body weight (left) and age (right) in the final population pharmacokinetic model (red, blue, green, yellow dots for infants, children, adolescents, adults' values respectively; the black line is a smooth through the data). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Drugs & Therapy Perspectives
https://doi.org/10.1007/s40267-019-00629-5

ADIS DRUG Q&A

Check for updates

Midazolam oral solution (Ozalin®): a profile of its use for procedural sedation or premedication before anaesthesia in children

Katherine A. Lyseng-Williamson[1]

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Abstract
Ozalin®, a novel oral solution of 0.2% midazolam, is an effective option for moderate sedation prior to a therapeutic or diagnostic procedure, and as premedication before anaesthesia, in infants, children and adolescents. Orally administered midazolam has a rapid onset and short duration of action, with well-established favourable efficacy, tolerability, safety and acceptability profiles in these indications. To overcome the problems of bitter taste and inconsistent bioavailability associated with extemporaneous formulations of oral midazolam, Ozalin, a commercially prepared oral midazolam formulation, contains the inert excipient γ-cyclodextrin, which forms inclusion complexes with midazolam, thereby enhancing the solubility and stability of midazolam solutions, and masking its bitter taste. Ozalin is administered at the lowest dose of midazolam (i.e. 0.25 mg/kg) that has been shown to be effective, with this dose providing sedative effects consistent with the historical data for midazolam at doses that were the same or higher (i.e. 0.5–1.5 mg/kg).

CONCLUSIONS Préparation spécifique vs galénique:

- Efficacité avec peu d'effets collatéraux
- Effet rapide et courte durée d'action (absorption 30', t1/2 : 2h)
- Dose efficace plus faible (0,25mg/kg)
- Risques faibles
- Effets toujours réversibles (flumazenil)
- Administration plus facile
- Goût agréable

Table 1 Summary of the prescribing information of midazolam 0.2% oral solution (Ozalin®) in the EU [ ]

What are the approved indications for Ozalin in children aged 6 months to 17 years?	
For moderate sedation before a therapeutic or diagnostic procedure	
As premedication before anaesthesia	
How is Ozalin available and how should it be stored?	
Availability	Single-dose ampoules containing 5 mL of midazolam 2 mg/mL oral solution (10 mg/ampoule)
	A single-use filter straw + a single-use oral applicator are provided for each ampoule
Storage	Store at room temperature (do not refrigerate, freeze or store at > 30 °C) in the original packaging
How should Ozalin be administered?	
Dose (based on actual body-weight)	0.25 mg/kg up to a maximum of 20 mg (even in children weighing > 80 kg)
Timing of administration	≈30 min before the procedure or anaesthesia
Preparation of dose (immediately before administration)	Using the filter straw, ampoule and oral applicator, fill the oral applicator to the graduation mark corresponding to the weight of the child in kg (applicator is graduated from 3 to 40 kg)
Administration (oral use only)	Empty the contents of the oral applicator into the child's mouth, child should swallow the contents immediately
How should Ozalin be used in high-risk patients?	
Patients with lung conditions	Chronic respiratory failure: use with caution (respiratory depression may be exacerbated)
	Severe respiratory failure, an anatomical abnormality of the respiratory tract or lung disease: use is contraindicated
Patients with chronic renal failure	Use with caution (midazolam or its metabolite may accumulate)
Patients with hepatic impairment	Mild or moderate impairment: use with caution (midazolam or its metabolite may accumulate); carefully monitor vital signs and sedative effects
	Severe impairment: use is contraindicated
Patients with heart failure	Use with caution (clearance of midazolam may decrease)
Patients in poor general health	Use with caution (patients have increased sensitivity to the CNS effects of benzodiazepines)
Patients with a history of alcoholism/drug addiction	Avoid use (in common with other benzodiazepines)
What are the other contraindications to the use of Ozalin?	
Hypersensitivity to midazolam, other benzodiazepines or any of formulation excipients, including γ-cyclodextrin, citric acid monohydrate, sucralose, ethanol (in the orange flavour), and sodium hydroxide; myasthenia gravis; sleep apnoea syndrome	
What clinically relevant pharmacokinetic drug interactions may potentially occur with midazolam?	
CYP3A4 inhibitors[a]	Plasma concentrations of midazolam may increase, leading to increased sedative effects; carefully monitor vital signs and sedative effects
	Exposure to midazolam may be effected for several days to several weeks after administration of a CYP3A4 inhibitor
CYP3A4 inducers[b]	Plasma concentrations of midazolam may decrease, leading to reductions in psychomotor effects
What clinically relevant pharmacodynamic drug interactions may potentially occur with midazolam?	
Alcohol (including alcohol-containing medications)	Strictly avoid concomitant use (increases sedation and the risk of clinically significant respiratory depression)
Other sedatives, hypnotics and CNS depressants	Avoid concomitant use (increases sedation and the risk of clinically significant respiratory depression)

CYP cytochrome P450

[a]Examples include azole antifungals, macrolide antibiotics, HIV protease inhibitors, histamine H_2 antagonists, fluvoxamine, verapamil, diltiazem, nefazodone, ivacaftor, atorvastatin, aprepitant, propiverine, grapefruit juice, *Echinacea purpurea*, turmeric rhizome

[b]Examples include rifamycin, carbamazepine, phenytoin, efavirenz, St. John's wort

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Retour d'expérience préliminaire

Hôpital pédiatrique La Timone Marseille

Contexte :

- Période: Mars 2021 – Mars 2022
- Population exposée : 17% des patients (1000 ampoules de midazolam solution buvable)
- Principaux services concernés:
  - chirurgies pédiatriques
  - onco-hématologie

Objectif : Evaluer l'impact de l'intégration d'une solution buvable de midazolam sur la pratique de la prémédication

Cible : Infirmières des services de l'Hôpital d'enfants de la Timone (via les cadres)

Les questions et les réponses

A votre avis

1) La solution buvable a-t-elle simplifié l'administration de la prémédication dans votre pratique quotidienne?
   OUI à 100 %*

2) Par rapport au midazolam IV dilué, la forme galénique buvable vous a-t-elle paru plus agréable pour les enfants?
   OUI à 100 %*

3) La disponibilité d'un applicateur dose/poids est-elle rassurante dans votre pratique professionnelle?
   OUI à 100 %*

4) La formulation buvable est-elle améliorable?
   En général elle va très bien, pour certains enfants le goût pourrait être encore améliorable.

*Réponses possibles : OUI / NON / JE NE SAIS PAS