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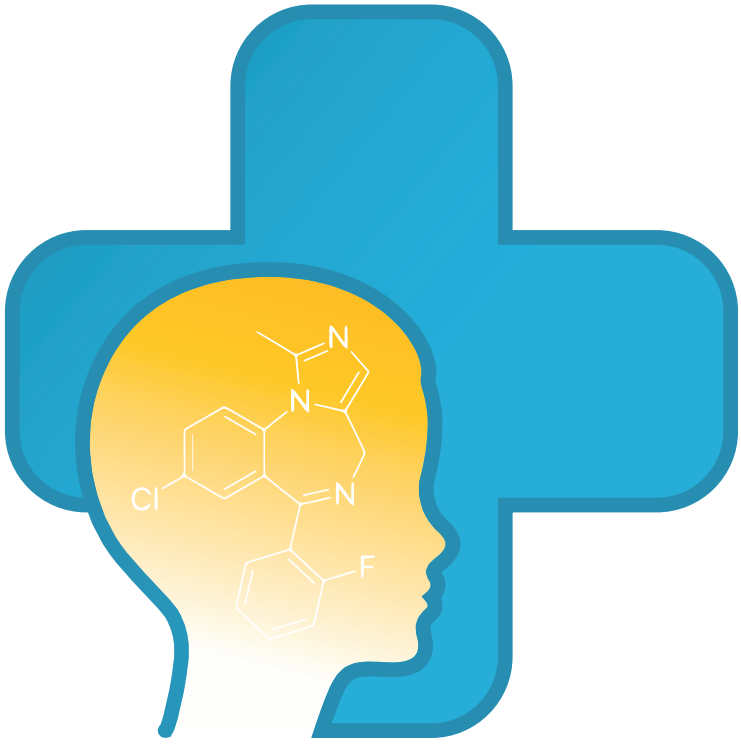

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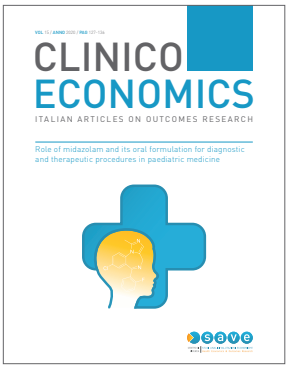

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Role of midazolam and its oral formulation for diagnostic and therapeutic procedures in paediatric medicine*

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ABSTRACT

In paediatric medicine, pharmacological sedation for diagnostic and therapeutic procedures and as premedication before the induction of anaesthesia is a topic of interest and discussion, due to the presence of still unmet medical needs. The use of midazolam as pre-anaesthetic or in the procedural analgosedation in paediatric patients is well established and considered safe and effective. However, at the moment, in Italy, the only authorised formulation of midazolam is by injection, to which the refusal by paediatric patients is commonly reported, requiring additional actions to complete the programmed or emergency procedures. Moreover, in hospital, the off-label use of extemporaneous oral solutions of midazolam (IV and IM vials) in paediatric patients is also well-documented. Also In this case the success of the therapy may be hindered by the bitter taste of the medication, leading to drug rejection by the patient or to its poor collaboration. Aiming at collecting data from current clinical practice in Italy, we created a survey in order to obtain specific information about paediatric analgosedation and about the methods and difficulties of administering sedative drugs for diagnostic/therapeutic procedure or as pre-anaesthetic agents. The survey, consisting of 10 questions, was administered from February to July 2020 to Italian clinicians of 19 centres located throughout the country. The results of the survey, containing the information of 2,255 patients, highlighted the presence of unmet medical needs for these patients, linked to the difficulties in the drug administration and the lack of an authorised oral formulation of midazolam for paediatric use. In particular, results showed that 1,732 (77%) subjects were treated for pre-anaesthesia and 523 (23%) for procedural intervention. Among the patients treated for pre-anaesthesia, 801 were treated for sedation (325 <6 years and 476 >6 years) and 931 for anxiolysis (329 <6 years and 602 >6 years). Among the patients treated for procedural sedation

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(523), 369 were treated for a programmed elective intervention, while the remaining 154 were treated in emergency. The results concerning the difficulty/delay in the administration of midazolam, reported in 47% of cases, were of interest. As a matter of fact, According to the results, due to the difficulties in the administration of the drug, in 39% of cases the intervention was postponed, in 32% of cases the therapy was changed and in the remaining 29% of cases a non-pharmacological action was adopted. Ultimately, the results of the survey showed the presence of important unmet medical needs related to issues in the drug administration and the lack of an authorised oral formulation for paediatric use. These conditions make it necessary the off-label use of extemporaneous oral formulations of midazolam with the favourable opinion of clinicians towards the administration of an oral formulation specifically authorised for paediatric use. The availability of such medication would respond to important unmet medical needs, representing an effective, appropriate and well tolerated therapeutic alternative for moderate sedation before diagnostic and therapeutic procedures and as premedication before the induction of anaesthesia in paediatric patients.

INTRODUCTION

In paediatric medicine, pharmacological sedation for diagnostic and therapeutic procedures and as premedication before the induction of anaesthesia is a topic of interest and discussion, due to the presence of still unmet medical needs. There are several levels of intensity in sedation. In general, pharmacological sedation induces a dose-dependent continuum of modifications in the state of consciousness, which ranges from a mild sedation-anxiolysis to a moderate and a deep sedation and to a general anaesthesia.[1] Each level of sedation is associated with changes in patient responsiveness and with an increased depression of respiratory and cardiovascular functions. The diagnostic and therapeutic procedures can be either non-invasive or invasive and, especially in the second case, be responsible of a deep anxiety in subjects undergoing such procedures, and even more so in paediatric subjects. In these patients, the state of anxiety, in addition to generating a severe suffering condition prior to the diagnostic/therapeutic procedure, is related to negative pre-, intra- and post-operative/procedural outcomes, such as: surgery cancellation and delay of treatments due to poor behavioural compliance,[2,3,4] the need for additional post-operative drugs, such as postoperative analgesics, due to increased levels of post-surgical pain,[3,5,6,7,8] delirium in emergency, that leads to an increased post-anaesthec care and hospitalisation,[2,3] and an increased incidence or severity of negative behavioural changes (nightmares, waking up crying, sleep or separation anxiety, apathy, eating disorders), which are particularly common after surgery in children.[5,9] Preoperative anxiety in children undergoing surgery is associated with a more painful and slower postoperative recovery and a higher incidence of post-operative sleep and behavioural disorders. Therefore, the non-optimal management of pre-operative/pre-procedural anxiety can lead to negative outcomes both for patients and patient care system. Thus, sedation procedure of paediatric patients prior to diagnostic and therapeutic procedures or anaesthesia has, as its main goals, the reduction of fear

and anxiety in the child, the reduction of discomfort and pain associated with the procedure, the improvement of adaptation to mechanical ventilation and the reduction of the risk of self-removal of invasive devices.[10,11,12] Finally, sedation is essential in order to protect the child during the clinical intervention and to control its actions for the safety and success of the procedure, especially in cases where the patient should not move or act (radiological imaging, echocardiography, radiotherapy). The most commonly used drugs for sedation are benzodiazepines and particularly, among these, midazolam. Midazolam is a short-acting benzodiazepine with a relatively high affinity for benzodiazepine receptors distributed in various regions of the central nervous system, presenting a rapid onset[13] and short duration of action that allow a rapid recovery. The efficacy and safety of midazolam used for sedation (alone or in combination with analgesia, other drugs or psychological techniques) are well-recognized in literature.[14] This drug has an established therapeutic role in sedation and procedural anaesthesia and exerts a well-documented anxiolytic and sedative actions. The therapeutic advantage for the patient is due to its relatively short duration of action, commensurate with the desired effect, its manageability in terms of dosage and, above all, the absence of negative effects after elimination, an effect that is all the more appreciable considering the paediatric target. Currently, midazolam is authorised in Italy for use as intravenous (IV) and intramuscular (IM) sedative drug. However, various equivalent drugs, originated from Ipnovel® 5mg/ml, are available. Therefore, there is no oral formulation with a paediatrically authorised dosage of this drug, despite the clinical off-label use of extemporaneous oral formulations of midazolam vials for IV/IM, in procedural and anaesthetic medicine, is known. The use of extemporaneous oral formulations is due to the need to overcome invasive or traumatic methods of administration, such as IV and IM, which generate anxiety, agitation and pain in patients. For these reasons, these formulations are often rejected by paediatric patients, typically uncooperative and known to hinder the planned procedures, sometimes requiring changing in therapy, the use of general anaesthesia or the postponement of the diagnostic/therapeutic intervention, with a negative impact in terms of general care and healthcare costs. Thereby, the oral administration is preferable to induce sedation and anxiolysis and successfully complete the medical or diagnostic procedures. However, also the off-label oral administration of extemporaneous solutions may encounter obstacles due to the particular bitter taste of midazolam. The international literature highlights the presence of important unmet medical needs in paediatric analgosedation, including the shortage of authorised paediatric medicines and the difficulty of administering intravenous or intramuscular formulations, often refused by paediatric patients, and leading to the off-label use of unauthorised medicinal products, with disadvantages and risks in terms of efficacy, safety and tolerability. In view of the fundamental role of midazolam in paediatric medicine for procedural or pre-anaesthetic sedation and the difficulties of administering this drug, there is an urgently need for an oral midazolam-based product specifically formulated and authorised for paediatric use in Italy. In light of these considerations, but in the absence of data from the real-world, we decided to conduct a survey of Italian clinicians in order to collect information from current clinical practice to support the use of any paediatric oral formulation of midazolam that can sustain the off-label use of this drug. At this regard, it might be interesting to consider the use of a paediatric oral formulation of midazolam recently registered in Italy, Ozased®. This is the first paediatric oral formulation of midazolam registered in Italy, indicated in children between 6 months and 17 years of age for moderate sedation for therapeutic or diagnostic procedures or as premedication before the induction of anaesthesia. Compared to the reference medicinal product Ipnovel® 5 mg/ml solution for injection/infusion and related equivalents on the market, it presents a different route of administration, pharmaceutical form and dosage and its indication for moderate sedation in the paediatric population has been restricted for a therapeutic or diagnostic procedure or as premedication

prior to anaesthesia, only. In order to authorise this new product, clinical studies have been conducted to demonstrate the therapeutic equivalence through data on bioavailability, pharmacokinetic profile, safety and tolerability in comparison to the reference product and to the orally administration of parenteral formulations of midazolam. The standardisation of an oral formulation of midazolam avoids problems related to the individual extemporaneous preparation of parenteral formulations, and provides a controlled, consistent and reliable oral formulation with known purity, solubility, stability and potency with an important limitation of unpredictable adverse events or of their severity. Ozased® requires a single dose oral administration of 0.25 mg/kg in children aged six months or more. The dose must be adjusted to the patient's weight and not exceed the maximum limit of 20 mg of midazolam (corresponding to 2 vials) even for children over 80 kg. The formulation, specifically developed for paediatric use, required the use of γ-cyclodextrin, an inclusion complex capable to mask the bitter taste of midazolam and to improve its solubility, thus making the product more tolerable for paediatric patients. Indeed, medicine acceptability plays a fundamental role for the success of the medical procedures, thus avoiding delay in the diagnostic and/or therapeutic procedures in the context of a special or programmed treatment. Therefore, the availability of a new oral formulation of midazolam, specifically developed for paediatric use, could be a valid therapeutic alternative able to provide an effective, safe and well tolerated medication in children for moderate sedation before therapeutic or diagnostic procedures and as premedication before the induction of anaesthesia.

MATERIALS AND METHODS

With the aim to collect data from current clinical practice in Italy, we created a survey in order to obtain specific information about paediatric analgosedation and about the methods and difficulties in administering sedative drugs for diagnostic/therapeutic procedure or as pre-anaesthetic agents. The survey, consisting of 10 questions, was administered from February to July 2020 to the Italian clinicians of 19 centres located throughout the country (Figure 1). Clinicians were asked to answer with a number, or a percentage value, based on their experience. Questions were aimed to identify: epidemiological data referring to the number and the age of patients undergoing sedation/anxiolysis, pre-anaesthesia, and procedural analgosedation; the frequency with which issues in the administration of midazolam to the patients have been observed; the frequency with which some actions have been taken to solve the problem; the frequency of administration of an extemporaneous midazolam-based oral formulation in paediatric patients and relative perception/tolerance. Finally, practitioners were asked for what percentage of patients could be assessed for an oral administration of midazolam specifically formulated for paediatric use, if available. For data analysis and processing, descriptive statistical measures, such as the identification of the minimum and maximum values, mean and variance, have been used.

RESULTS

Table 1 reports the questions administered to clinicians and the relative collected results. The research involved

FIGURE 1
Italian clinic centres involved in the study

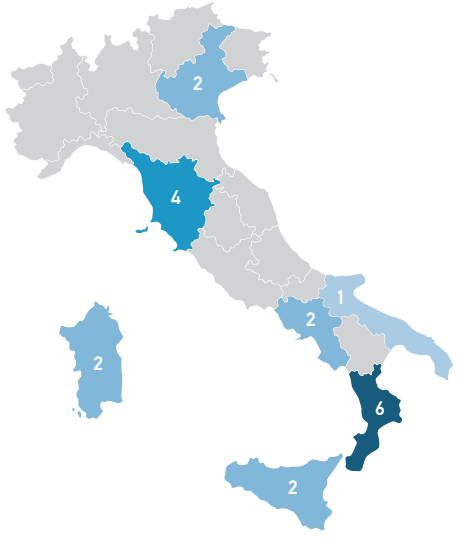

TABLE 1
Questions administered to clinicians and the relative results

Questions	N	%
1. In the last 30 days, at your centre, how many paediatric patients have done treatment for:		
A. Anaesthetic premedication	1732	77%
B. Procedural analgosedation	523	23%
Total patients	2255	
2. How many patients treated for pre-anaeststhesia were treated for sedation	801	46%
How many of these are under 6 years old	325	41%
How many of these have been treated with midazolam	249	77%
How many of these are over 6 years old	476	59%
How many of these have been treated with midazolam	401	84%
3. How many patients treated for pre-anaeststhesia were treated for anxiolysis	931	54%
How many of these are under 6 years old	329	35%
How many of these have been treated with midazolam	270	82%
How many of these are over 6 years old	602	65%
How many of these have been treated with midazolam	459	76%
4. How many of the patients listed in question 1B received a procedural sedation for an *elective intervention*	369	71%
How many of these have been treated in the interventional area	206	56%
How many of these have been treated with midazolam	173	47%
5. How many of the patients listed in question 1B received a procedural sedation for an *emergency intervention*	154	29%
How many of these have been treated with midazolam	90	58%
6. Given the current indications for the administration of midazolam in paediatric patients, from your experience, how many patients have presented resistance/delay in the administration of the drug?		47%
7. In the patients listed in question 6, among the following actions, which one is usually taken?		
Delay, postponement of the procedure		39%
Change medication (specify which one)		32%
Non-pharmacological action		29%
8. Based on your current clinical practice, have you ever administered an extemporaneous oral formulation of midazolam?		
Yes		73%
No		27%
9. If yes, it was:		
Accepted		51%
Spat		41%
Vomited		8%
10. If a paediatric oral formulation becomes available, how many patients would you administer it to?		78%

clinicians of 19 different centres located throughout the country and provided information about the treatment of 2,255 paediatric patients, referring to the month preceding the survey. Specifically, results showed that 1,732 (77%) subjects were treated for pre-anaesthesia and 523 (23%) for procedural intervention. Among the patients treated for pre-anaesthesia, 801 were treated for sedation (325 <6 years and 476 >6 years) and 931 for anxiolysis (329 <6 years and 602 >6 years). Among the patients treated for procedural sedation (523), 369 were treated for a programmed elective intervention, while the remaining 154 were treated in emergency. The survey provided the percentage of patients treated with midazolam in the group treated for pre-anaesthe-

sia, either for sedation or anxiolysis, and in the group treated for analgosedation, distinguishing, within the first group, the percentage of population under or over 6 years of age. Overall, these results concerning the clinical use of midazolam highlight its wide use in paediatric patients treated both for pre-anaesthesia and procedural analgosedation, confirming that, in most of clinical cases, midazolam is considered the best therapeutic choice. A very interesting data emerging from the survey, concerns the percentage of cases in which the administration of midazolam encountered resistance or delay. For instance, on the basis of their experience, clinicians reported difficulty/delay in administration in 47% of cases. Therefore, in about half of the cases, the administration has been hampered, making it necessary to take additional actions to address this issue. Indeed, according to the survey, as a results of the difficulty in the drug administration, in 39% of cases the intervention was postponed, in 32% of cases the therapy was changed and in 29% of cases a non-pharmacological action was taken, such as psychological support and correction of stressful environmental factors to reassure the patient and make him more collaborative. Moreover, clinicians were asked to provide feedback on their experience, referring to current clinical practice, of administering extemporaneous midazolam-based oral formulations. In 73% of cases a positive answer was given to this question, highlighting a wide off-label oral administration of midazolam for paediatric sedation. Referring to the question on the degree of tolerability/acceptance of the extemporaneous oral solution by the patients, it was found that this formulation is acceptable in 51% of cases, spat in 41% of cases and vomited in 8% of cases, with an overall rejection/ refusal rate of 49%. Finally, practitioners were asked to express their own opinion on the possibility of administering any oral formulation authorised for paediatric use. The Results to this question showed that, if available, clinicians were in favour of administrating an oral formulation of midazolam, specifically formulated and authorised for paediatric use, in 78% of patients.

DISCUSSION

This analysis intended to provide a focus on the topic of paediatric sedation for diagnostic and therapeutic procedures and as a pre-anaesthetic medication, by referring to data from current clinical practice in Italy, with the aim to highlight the presence of significant unmet clinical needs and potential new therapeutic alternatives. The results of the survey administered to clinicians confirmed the extensive use of midazolam in paediatric sedation. This result is in line with what has been reported and recommended in literature, according to which the use of this drug is well established in therapy and considered effective and safe compared to standard treatment, isolated analgesia, other sedative drug, psychological techniques or general anaesthesia.[14] The results reveal an interesting finding regarding the difficulty in administering midazolam in procedural analgosedation and as pre-anaesthetic. Indeed, 47% of cases reported resistance or delay in drug administration, thus implicating the consequent need of actions aimed at solving this issue and at ensuring the success of the programmed or emergency diagnostic/therapeutic procedure. Currently available midazolam formulations for sedative use are invasive and/or generally unwelcome and often not accepted by paediatric patients, who are typically uncooperative and prone to anxiety and preoperative/procedural agitation. Clinicians reported that, in most cases, the rejection of therapy requires a postponement of the procedures (39%) or a change of therapy (32%) or, in the remaining cases, non-pharmacological interventions that include strategies to manage the psychological factors of pain, anxiety and fear and to correct stressful environmental factors. The difficulties related to the administration of currently authorised midazolam formulations can directly lead to the off-label administration of oral formulations of midazolam (IV/IM vials in extemporaneous solution), with disadvantages and risks in terms of efficacy, safety and tolerability. Accordingly, the results of the survey confirmed that in 73% of cases clinicians administered an extemporaneous oral formulation of midazolam. Oral administration is certainly more accepted by paediatric

patients and therefore it is considered as a valid alternative by clinicians. However, even in this case, the correct administration of the drug may be hampered by the unpalatable taste of midazolam in solution. Considering the administration of extemporaneous oral formulations of midazolam, clinicians reported patient satisfaction in only 51% of cases, while in 41% and 8% of cases, the solution was spat and vomited, respectively. Therefore, the off-label use of oral formulations does not solve the problem linked to the difficulty in administering midazolam for paediatric sedation, thus keeping open an unmet medical need for this category of patients. In fact, in about half of the cases, the correct administration of the therapy, within the appropriate timescales to proceed with the programmed diagnostic/therapeutic or emergency actions, is not guaranteed by the currently available IV/IM formulations and difficulties with the off-label use of extemporaneous oral formulations are also reported. In line with this unmet medical need, by analysing the feedbacks of the clinicians interviewed, it appears clear that they are in favour of an oral formulation specifically formulated for paediatric use, if available. The results of the survey, in fact, show a propensity of clinicians to use an authorised paediatric oral formulation of midazolam in 78% of patients. This analysis has made it possible to analyse the critical issues related to some paediatric unmet medical needs, such as the difficulty of administering invasive formulations (IV/IM) often refused by the patient and the lack of authorised paediatric formulation, resulting in the off-label use of unauthorised medicinal products, with relative disadvantages and risks. Indeed, many of the medications currently used for analgosedation have not been authorised by AIFA for use in all or some paediatric age groups, despite the availability of efficacy data in literature.[1] In this case, the paediatric patient remains a "therapeutic orphan" due to the few clinical trials conducted for this category of subjects.[15] Moreover, despite the European Paediatric Regulation and the several initiatives undertaken by the Italian Medicines Agency (AIFA), only one third of the medication available for adult still reach the paediatric patient, and sometimes after many years.[16] AIFA and the Italian Society of Palliative Care, with the support of a dedicated working group, have drawn up a document that brings together the scientific evidences available to support the off-label use of medicines most frequently used in paediatric palliative care, with the aim to recognise the off-label use of these drugs. This is a step towards a better and more qualified care in several healthcare contexts, from hospital to home care. It would be desirable to monitor the use of these drugs in current clinical practice in order to characterise their overall profile and potential benefits.[17] Although recognition of the off-label use of certain medicines in paediatric care represents an important progress, it would also be important to encourage the development of medicines specifically formulated and authorised for paediatric use, in order to better protect this category of patients by offering therapeutic solutions that are more effective, safe and well tolerated. In this context, focusing once again the attention on paediatric sedation for diagnostic/therapeutic procedure or as a pre-anaesthetic agent, the availability of a midazolam-based medication, orally administrable, and specifically formulated for paediatric use, such as Ozased®, could represent an important therapeutic alternative, capable to respond to important unmet medical needs, overcoming the difficulties related to the injective administration of this drug and to the off-label oral administration of extemporaneous solution of midazolam (IV/IM vials). A greater medicine acceptability would result in a better management of pre-anaesthetic and procedural sedation, leading to a greater efficacy of therapy and a greater success of programmed or emergency procedures, with positive implications in terms of improving the medical care provided to the patient and reducing the costs due to failed administration. In light of these considerations, it would be interesting to evaluate the economic impact, for the Italian national health service (Servizio Sanitario Nazionale, SSN), of the failure of paediatric sedation with IV/IM administration of midazolam and of the off-label use of midazolam extemporaneous oral solution (IV/IM vials), as well as to assess

the potential economic benefits of using a specifically developed oral formulation of midazolam for paediatric use. National data estimates 228,000 paediatric surgical patients to which should be added 68,848 patients undergoing diagnostic procedures, for a total of 296,848 patients per year for whom procedural/pre-anaesthetic sedation can be considered.[18] Assuming to consider a percentage of use of any authorised paediatric oral formulation of 78% to this segment of population, according to the results of the survey, the sedation of 230,824 patients could be better managed than how it is currently possible with the available medications, thus facilitating the execution of the medical procedure (diagnostic/therapeutic/surgical) in safety, without burdening the load of iatrogenic negativity in the paediatric subject. Based on our knowledge, this is the first survey conducted in Italy aimed at providing data from current clinical practice for paediatric analgosedation, specifically referring to: the role of sedation with midazolam, the critical issues currently associated with the administration of this drug and the potential benefits of using an authorised oral paediatric formulation of midazolam. Although this study presents the typical limitations of a survey analysis and the data collection covers only a sample of centres and patients at a national level, we firmly believe that the information emerging from this study is in line with those already identified in literature, confirming the wide use of midazolam in paediatric sedation and the high percentage of failure of administration due to patient rejection. Moreover, this analysis provides information about the actions taken after the failure of the administration of midazolam and, above all, confirms the wide off-label use of extemporaneous oral formulations of midazolam and the clinicians' favourable propensity to administer an authorised paediatric oral formulation of this drug, if available in Italy.

CONCLUSIONS

Nowadays, the use of midazolam in paediatric procedural analgosedation or as premedication before the induction of anaesthesia is well-established and considered effective and safe. However, at the moment, in Italy, the only authorised formulation of midazolam is by injection, to which the refusal by paediatric patients is commonly reported, thus requiring additional actions (change of therapy, waiting or postponement of the previously planned medical procedures, non-pharmacological actions) to complete the planned or emergency procedures. The off-label use in hospitals of extemporaneous oral formulations of midazolam (IV/IM vials) in paediatric patients is well-documented. Also in this case, the success of the therapy may be hampered by the bitter taste of the medication, leading to the drug rejection by the patient or to its poor collaboration. These data were confirmed by the results of the survey administered to practitioners of 19 centres located throughout Italy, which provided information on 2,255 paediatric patients undergoing sedation for pre-anaesthesia or procedural analgosedation. The results of the survey highlighted the presence of important unmet medical needs for these patients, linked to the difficulty in administering this drug and the lack of an oral formulation specifically authorised for paediatric use. These conditions make it necessary the off-label use of extemporaneous oral formulations of midazolam with the favourable opinion of clinicians towards the administration of an oral formulation specifically authorised for paediatric use, if available. The availability of such medication would respond to important unmet medical needs, representing an effective, appropriate and well tolerated alternative for moderate sedation before diagnostic and therapeutic procedures and as premedication before the induction of anaesthesia in paediatric patients.

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