

A mini-review of non-parenteral clonidine preparations for paediatric sedation

Sara M Hanning^{1*}, Mine Orlu Gul¹, Irmgard Toni², Antje Neubert² and Catherine Tuleu¹, on behalf
of the CloSed Consortium

1 Department of Pharmaceutics, UCL School of Pharmacy, London, UK

2 Department of Paediatrics and Adolescent Medicine, University Hospital Erlangen,
Erlangen, Germany

**Corresponding author:*

Sara Hanning

Department of Pharmaceutics

UCL School of Pharmacy

29-39 Brunswick Square

London WC1N 1AX

United Kingdom

Phone: +44 (0)20 7753 5846

Email: s.hanning@ucl.ac.uk

Other authors:

Mine Orlu Gul

Department of Pharmaceutics, UCL School of Pharmacy, London WC1N 1AX, United Kingdom

Phone: +44 (0) 20 7753 5968

Email: m.gul@ucl.ac.uk

Irmgard Toni

Department of Paediatrics and Adolescent Medicine, University Hospital Erlangen, Erlangen,
Germany

Phone: +49 (0) 9131 85-41100

Email: irmgard.toni@uk-erlangen.de

Antje Neubert

Department of Paediatrics and Adolescent Medicine, University Hospital Erlangen, Erlangen,
Germany

Phone: +49 (0) 9131 85-41203

Email: antje.neubert@uk-erlangen.de

Catherine Tuleu

Department of Pharmaceutics, UCL School of Pharmacy, 29-39 Brunswick Square London
WC1N 1AX, United Kingdom

Phone: +44(0)2077535857

Email: c.tuleu@ucl.ac.uk

Abstract

Objective

To provide an overview of non-parenteral clonidine formulations and assess the feasibility of their use for paediatric sedation.

Methods

A literature search was conducted using electronic databases and a combination of search terms. Forty articles met the inclusion criteria. Publications were grouped into different dosage forms and assessed for their potential application for sedation of children in intensive care.

Key findings

Several routes of clonidine administration have been investigated for numerous indications in children, including perioperative sedation and analgesia. These include oral liquids, tablets, oral transmucosal systems, nasal sprays and rectal suspensions. Conflicting studies on oral transmucosal clonidine formulations suggest that further research is required to fully establish efficacy. Nasal sprays and rectal suspensions have the advantages of rapid onset of action and potential for dose flexibility, but predictable absorption is difficult to obtain.

Conclusions

Provided age-appropriate strengths are available, IV formulations remain the most predictable in terms of bioavailability and flexible in terms of dose adjustment. However, as with all routes, down-titration is difficult given the long half-life of clonidine. Oral transmucosal systems, nasal sprays and rectal suspensions have potential in a less acute setting, but significant clinical work is required to elucidate a full pharmacokinetic and pharmacodynamic profile.

Key words

Clonidine, formulation, paediatrics, non-parenteral, paediatric sedation

Introduction

Clonidine hydrochloride is commonly used off-label in paediatric anaesthesia and intensive care medicine. It acts by reducing intraoperative anaesthetic requirements and metabolic responses to surgery due to its effects on central sympathetic outflow and centrally based analgesia mechanisms.[1] Clonidine is recommended for the sedation of critically ill children in Paediatric Intensive Care Units (PICUs) by the United Kingdom and German consensus guidelines,[2; 3] as well as in clinical guidelines used at hospitals across Europe.

Clonidine hydrochloride is an imidazoline α -2 adrenoceptor agonist. It is licensed in adults for the treatment of hypertension, migraine and menopausal flushing.[4] It has an aqueous solubility of about 77 mg/mL[5] and is considered either Class I (high solubility/high permeability) or Class III (high solubility/low permeability) under the Biopharmaceutics Classification System (BCS).[6] Although clonidine is sometimes classified as a BCS Class III drug, many years of successful therapy in hypertensive adults as a solid oral dosage form would suggest that permeability does not limit oral bioavailability. In the United Kingdom, clonidine is available in tablets (25mcg), ampoules for injection (150mcg/1mL) and as a transdermal delivery system that delivers 0.1, 0.2, or 0.3 mg clonidine per day.[7] However, much smaller intravenous infusion doses are required for sedation in children. A limited dose finding study in PICU has shown an intravenous infusion rate of 1-2 mcg/kg/h provides dose dependent sedation without haemodynamic compromise in terms of heart rate, blood pressure or cardiac output.[8]

Rapid and effective sedation is often required in an emergency paediatric setting. Consequently, delivery is often by the intravenous (IV) route.[9] An advantage of IV drug delivery is that the dose immediately enters systemic circulation and can be adjusted by altering the flow rate of an IV pump. This means that loading doses and maintenance doses can be continuously administered. However, as clonidine is not licensed for this indication, there are no age-specific formulations available. To address this, a large, multi-centre clinical trial investigating clonidine for the sedation of paediatric patients in the intensive care unit (CloSed project, see ClinicalTrials.gov, ref. NCT02509273) is currently underway and age-appropriate formulations have been developed (<http://www.closed-fp7.eu>). However, in a less acute setting IV drug delivery is not always ideal, particularly for children already subject to the stress of a hospital environment. This review aimed to explore alternative, non-injectable clonidine formulations that have been developed and their feasibility as candidates for use in the sedation of children. By highlighting possible formulations and knowledge gaps pertaining to these, novel alternatives will be identified in the hope that a less

invasive clonidine formulation may be developed for the sedation of children in an emergency setting.

Method

Search strategy

To determine the types of clonidine formulations used for sedation, relevant journal articles written in English between January 1946 and December 2014 were considered. Reviews, conferences and book citations were excluded so only original research articles and case reports were eligible for inclusion. Three databases - Scopus, OvidSP (including Embase and Ovid Medline) and Web of Science were searched using the independent keywords 'clonidine' AND 'drug administration', with subject headings: 'Drug administration' OR 'inhalational drug administration' OR 'intradermal drug administration' OR 'intranasal drug administration' OR 'oral drug administration' OR 'rectal drug administration' OR 'sublingual drug administration' OR 'topical drug administration' OR 'transdermal drug administration'. These searches were then combined and duplicates were removed.

Eligibility criteria and process of selection

The title and abstract of each publication was screened. Publications were excluded if the route of administration was by injection or if the dosage form was a commercially available unmodified tablet (unless the population group was paediatric), because the focal point of this review was to assess the feasibility of alternate clonidine dosage forms for the sedation of children. If the dosage form or route of administration was not specified, then the indication was assessed and studies of hypertension, opioid withdrawal or growth hormone response were excluded on the basis that they were likely to use commercially available dosage forms. Publications that did not involve a clonidine formulation were also excluded.

Data extraction and analyses

Dosage form, route of administration, dose, number of subjects and age range, excipients (if listed) and indication of each of the selected publications were recorded. Following the screening process, the full-texts of publications that met the criteria were examined and a second screening step took place. Publications were grouped and dosage forms were assessed for their potential application for sedation of children in an intensive care setting.

Non-parenteral clonidine preparations

The title and abstract of 3978 publications were screened and from these, the full-texts of 66 publications were assessed for eligibility following the criteria stated above. After 26 papers were

excluded for being outside of the parameters of interest, 40 remained and were included in the final review.

This literature review involved a lengthy screening process, with 3978 studies initially screened for inclusion. Though it would have been ideal to reduce this large number of hits, this proved difficult because automatically omitting certain key words, such as ‘intravenous’ excluded all studies, including those comparing intravenous clonidine administration with alternative dosage forms. In addition, in many of these studies the route of clonidine administration was not a focal point of the publication and therefore, not specified in the title or abstract. This made the initial screening phase a lengthy process that required some assumptions, resulting in the exclusion of studies of hypertension, opioid withdrawal or growth hormone response where dosage form or route of administration was not specified on the basis that they were likely to use commercially available dosage forms.

A summary of the different clonidine dosage forms is presented in Table 1. The following sections discuss these dosage forms in further detail.

Oral route

Orally, clonidine is well absorbed with good central nervous system penetration. However, a major limitation of oral clonidine for the sedation of children in a hospital setting is its slow onset of action, with peak plasma concentrations being reached after 60 to 90 minutes.[51]

Oral tablets

Many children are unable to swallow ‘adult size’ tablets[52-54] and this is augmented in an intensive care setting. Previous studies investigating the use of clonidine tablets in children have tended to focus on older individuals and chronic conditions.[15; 16; 19; 20] Mini tablets (around 4mm diameter) have shown promise as dosing platforms for children.[55-57] Recent research has shown that full-term neonates aged between 2 and 28 days accepted uncoated mini tablets equally well as syrup.[58] However, to date there have been no papers published on the use of small-sized tablet formulations for clonidine. Such a formulation would need to cater for children of a wide weight range, and the consumption of multiple tablets would be unavoidable. In addition, onset of action remains a limitation and in an intensive care setting, even swallowing mini tablets may not be possible.

Oral liquids

Several studies have investigated liquid formulations of clonidine hydrochloride.[21; 22; 24-35] Various sources of clonidine have been used, as well as a range of sweeteners to improve

palatability (Table 2). Oral liquid formulations have the advantage of dose flexibility but excipients are required to mask the taste of the drug. When extemporaneously compounding any formulation, the risk for error is greatly increased. For example, one case study reported a five-year-old child who received a 1000-fold overdose of clonidine due to a calculation error when formulating an oral liquid.[59]

Although oral liquids have been used perioperatively in children, their major limitation is slow onset of action. Mahajan and colleagues found that although the quality of sedation was superior with clonidine as opposed to midazolam, onset of sedation was significantly slower, at 38.5 ± 12.6 minutes.[26] Larsson and co-authors found that the maximum plasma concentration following administration of 4mcg/kg clonidine in an apple fruit drink was 0.77mcg/L (T_{max} 1.04 hours). Oral bioavailability in children aged 3 to 10 years old was found to be 55.4% (CV 6.4%; 95% CI 0.469, 0.654), which is lower than adults.[28] This has implications for the dosing regimen, meaning that higher doses would need to be administered in order to achieve a therapeutic effect comparable to IV administration.

Arenas-López et al. studied the relationship between oral dose via nasogastric tube, plasma-profile and sedative effects in 24 children (median [interquartile range] age 3 months [1.3-15.9], weight 5.0kg [4.5-5.6]) requiring intubation for primary respiratory failure and likely to need mechanical ventilation for longer than 72 hours in the PICU.[23] The clonidine dose range used in this study was 3-5mcg/kg, which was extrapolated from previous paediatric premedication studies [60] and adult schedules on a dose/kg basis. This produced an initial temporal increase in plasma concentration that appeared to plateau by 41 hours, suggesting that steady state values were achieved by this time. Clonidine was administered as an oral solution that was manufactured under a Medicines & Healthcare Products Regulatory Agency (MHRA) “specials” manufacturing licence, but it was not stated whether clonidine was obtained from raw powder, crushed tablets or the commercially available IV formulation.

Oral transmucosal route

Oral transmucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Oral transmucosal drug delivery bypasses hepatic first pass metabolism and avoids degradation or metabolism by gastric juices and enzymes in the gastrointestinal tract.[61] The oral mucosa has a relatively high permeability and abundant blood supply, which allows for rapid transport to the systemic circulation.[62] For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route

compared with the intravenous route. However, in order to be successful for transmucosal drug delivery, a drug candidate must have good lipophilicity and high water solubility at physiological pH. Irritancy to the oral cavity can also be a problem. Clonidine is lipophilic and as such, has the potential to be delivered by this route. In addition, the concentration required for therapeutic effect is in the microgram range, meaning that drug loading would not be a problem. However, developing strengths that consider the wide body weight range of paediatrics, from birth up to 18-year-olds, as well as loading doses and dose changes, is challenging with single use solid dosage forms and requires careful consideration.

Clonidine lollipops have been investigated for their potential as pre-anaesthetic medication.[36; 37] One study found that satisfactory sedation was achieved in ten out of 16 patients but that patients aged 1-3 years were unable to consume a sufficient dose for adequate sedation.[36] In addition, the time taken to consume a lollipop could be variable between patients. A further study found that orally disintegrating tablet formulations were superior to lollipops in reaching satisfactory sedation.[37] A summary of oral transmucosal formulations identified in the literature search are presented in Table 3.

Sublingual tablets have been considered as an alternative to oral administration for adults with hypertension.[38; 39] Gilkeson and Delaney suggested that the apparent effectiveness, simplicity and safety of sublingual clonidine would make it a useful alternative in the treatment of hypertension.[39] Cunningham and colleagues found that although clonidine was well absorbed sublingually, the pharmacokinetic and pharmacodynamic profiles were not significantly different from the oral route, meaning that the onset of action was still between 60 and 180 minutes.[38]

Lollipop formulations identified in this literature search were sweetened with sucrose and starch syrup, but excipients used to improve the palatability of the ODTs and sublingual tablets were not described.[36; 37] No study provided data on taste acceptability from patients. In addition, studies involved children over the age of 12 months and the sample sizes in each study were small (Table 3). Further research into oral mucosal clonidine formulations is required to fully establish efficacy.

Rectal route

Another enteral route, the rectal route, has many advantages in the delivery of medicines to children because there is no need to swallow or mask the taste of the dosage form. However, there are also challenges associated with the development and use of rectal drug formulations, which may explain the paucity of commercially available rectal preparations.[63] Rectal administration can lead to

erratic absorption and because of this, must be fully evaluated for safety and efficacy in addition to bioavailability studies. Further, there are issues surrounding patient perception, including cultural barriers, understanding and attitudes.[64; 65]

Clonidine has been rectally administered by diluting a commercial IV solution (Catapresan, 150 mcg/mL) in normal saline to 10 mcg/mL before administering using a syringe adapted to a cut suction catheter. Following administration of 2.5 mcg/kg clonidine to ten children (14-48 months old weighing 10-20kg), leaking of the solution was not a problem and a high bioavailability (95%) was demonstrated. The median maximum plasma concentration was 0.77ng/ml, half-life was 12.5 hours and volume of distribution 0.961 L/kg.[43]

Peak plasma concentrations are reportedly reached 40-50 minutes following rectal clonidine administration.[66] This has been supported by a case study in an adult that reported crushed clonidine tablets mixed with sorbitol and given rectally via a catheter effectively controlled hypertension, with an initial response noted within 45 minutes.[44] The development of a liquid suspension administered by a catheter allows for easy dose adaptation, compared to semi-solid dosage forms (such as suppositories), which do not allow dose flexibility. However, sorbitol is an osmotic laxative and therefore, not an appropriate vehicle for a rectal suspension.

Nasal route

Intranasal drug administration is an easy and relatively non-invasive method of drug administration that avoids hepatic first pass metabolism. The nasal cavity consists of thin, vascularised epithelium, offering fast absorption and rapid onset of therapeutic effect for many drugs. Babhair and colleagues compared the bioavailability of IV and nasal clonidine in rodents and found that peak plasma concentration via the nasal route was reached within ten minutes.[48] However, Almenrader and colleagues compared an oral liquid formulation of clonidine with nasal drops and found that although sedation was equivalent in the two groups, nasal drops resulted in a slower onset of action.[21] In addition, it may be difficult to control the dose of drops administered, which could result in altered absorption. The use of an aerosol spray for intranasal delivery has been shown to be preferable, likely as a result of the superior spread of the drug into the nasal cavity and subsequent improved absorption.[45] Clonidine hydrochloride is highly water soluble, so theoretically a high concentration would be feasible. However, direct transport of clonidine from the nasal mucosa into systemic circulation has been shown to be unpredictable and erratic.[47] Further, the volume of drug that can be administered intranasally is limited and may be a factor in variability. The maximum volume for adults is 100-200 µL per nostril, but this is likely to be considerably smaller

and more varied in children. Excess fluid would run out of the nose and be lost, or flow down the back of the throat and essentially undergo metabolism via the oral route. In addition, several factors including drug dose, preparation, method of administration, state of the nasal mucosa and definition of sedation may play a role in the variation seen across studies.[46]

Larsson and colleagues found that nasal aerosol clonidine delivery at a concentration of 3-8 µg/kg did not result in sufficient preoperative sedation within 30 minutes of sedation,[45] yet other studies of similar concentrations found that sedation was adequate within 30 minutes.[21; 22; 46] In summary, further research is required to ascertain the dosing regimen required to achieve sufficient sedation within 30 minutes.

Pulmonary route

The inhaled route of clonidine administration has been investigated for its effect on bronchoconstriction. Although animal studies have shown promise for this indication, to date human studies have not, possibly due to differences in the neural control pathways.[49] Systemic effects of inhaled clonidine such as sedation and hypotension were not reported, so the impact of inhaled clonidine on sedation is not currently known. If it is possible to achieve sedation by pulmonary clonidine delivery, administration may be achieved by nebulisation.

Transdermal route

The literature search resulted in a paucity of transdermal formulations. Transdermal clonidine is licensed for the treatment of hypertension and the lack of hits was most likely due to the exclusion of hypertension studies on the basis that the focus of this review was on the formulation and testing of (in particular extemporaneous) clonidine preparations for use in children. The safety and efficacy of the commercially available clonidine transdermal system has not been established in paediatrics, though it has been reportedly used off-label for the management of hypertension, Attention deficit hyperactivity disorder (ADHD) and neuropathic pain.[67] The patches are programmed to release clonidine at an approximately constant rate over a seven-day period, and the absence of rebound hypertension after the patch is removed suggests that following application, a depot of clonidine in the skin becomes a self-tapering source.[68] This is not ideal when sedation is no longer required. Further, it takes up to four days to achieve steady state plasma concentrations,[67; 68] so is not a feasible dosage form for acute sedation.

Conclusions

Several different routes of clonidine administration have been investigated for numerous indications in children, including perioperative sedation and analgesia. This report discussed the feasibility of alternative, less invasive dosage forms in a paediatric intensive care setting, where the IV route is common. Oral liquid dosage forms have potential as alternatives to IV administration of clonidine in an intensive care setting, offering reasonable dose flexibility and individualisation despite their slower onset of action. However, the patient must be conscious in order to swallow the liquid. Oral tablets do not allow dosing flexibility and are not suitable for young children. Clonidine has the potential to be delivered via the oral transmucosal route, but appropriate strengths need to be elucidated and further formulation studies are required to ensure appropriate taste masking. Nasal sprays and rectal suspensions have the advantage of rapid onset of action and potential for dose flexibility. In addition, dosing may be maintained while the child is sedated. IV formulations remain the most flexible in terms of dosage accuracy and control, and are the easiest to administer in an intensive care setting. Significant formulation work is required to develop an effective dosage form and elucidate a full pharmacokinetic and pharmacodynamic profile of clonidine administered via all of these routes.

Acknowledgements

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 602453.

References

1. Nishina K et al. Effects of oral clonidine premedication on plasma glucose and lipid homeostasis associated with exogenous glucose infusion in children. *Anesthesiology* 1998; 4: 922-927.
2. Martin J et al. Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care - short version. *Ger Med Sci* 2010: Doc02.
3. Playfor S et al. Consensus guidelines on sedation and analgesia in critically ill children. *Intensive Care Med* 2006; 8: 1125-1136.
4. Joint Formulary Committee. *British National Formulary*, 57th edn. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2008.
5. O'neil MJ ed. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, Cambridge: Royal Society of Chemistry, 2013.
6. Dahan A et al. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. *AAPS J* 2009; 4: 740-746.
7. Datapharm. *Electronic Medicines Compendium (eMC)*, Leatherhead, UK, 2016. <https://www.medicines.org.uk/emc/search> (accessed 07 March 2016).
8. Ambrose C et al. Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability. *Br J Anaesth* 2000; 6: 794-6.
9. Sasada M, Smith S. *Drugs in Anaesthesia and Intensive Care*, 3rd edn. Oxford: Oxford University Press, 2003.
10. Wolf A et al. Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children:

- the SLEEPS (Safety profile, Efficacy and Equivalence in Paediatric intensive care Sedation) study. *Health Technol Assess* 2014; 71.
11. Schmidt AP et al. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Pediatr Anesth* 2007; 7: 667-674.
 12. Jahromi S et al. A comparison of the effect of oral paracetamol and clonidine on pediatric preoperative anxiety in adenotonsillectomy. *Pak J Med Health Sci* 2009; 3: 458-461.
 13. Qteshat BS. Use of oral clonidine and oral midazolam as preanesthetic medications in the pediatric patient undergoing tonsillectomy. *RMJ* 2011; 2: 114-115.
 14. Shiga M et al. Oral clonidine premedication does not change efficacy of simulated epidural test dose in sevoflurane-anesthetized children. *Anesthesiology* 2000; 4: 954.
 15. Fagermoen E et al. Clonidine in the treatment of adolescent chronic fatigue syndrome: a pilot study for the NorCAPITAL trial. *BMC Res Notes* 2012; 1: 418.
 16. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002; 4: 527-36.
 17. Nair V, Mahadevan S. Randomised controlled study-efficacy of clonidine versus carbamazepine in children with ADHD. *J Trop Pediatr* 2009; 2: 116.
 18. Schvehla TJ et al. Clonidine therapy for comorbid attention deficit hyperactivity disorder and conduct disorder: preliminary findings in a children's inpatient unit. *South Med J* 1994; 7: 692-5.
 19. Ming X et al. Use of clonidine in children with autism spectrum disorders. *Brain Dev* 2008; 7: 454-460.
 20. Jaselskis CA et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol* 1992; 5: 322-327.
 21. Almenrader N et al. Steal-induction after clonidine premedication: a comparison of the oral and nasal route. *Pediatr Anesth* 2007; 3: 230-234.
 22. Mukherjee S et al. Clonidine premedication for paediatric patients: A comparison of the oral and nasal route. *J Anaesthesiol Clin Pharmacol* 2010; 3: 319-322.
 23. Arenas-López S et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med* 2004; 8: 1625-1629.
 24. Mikawa K et al. Attenuation of the catecholamine response to tracheal intubation with oral clonidine in children. *Can J Anaesth* 1995; 10: 869-74.
 25. Almenrader N et al. Premedication in children: a comparison of oral midazolam and oral clonidine. *Pediatr Anesth* 2007; 12: 1143-1149.
 26. Mahajan RK et al. Comparison of oral clonidine and midazolam as premedications in children. *J Clin Diagn Res* 2012; 5: 870-873.
 27. Trevor S et al. A comparison of midazolam and clonidine as an oral premedication in pediatric patients. *Saudi J Anaesth* 2012; 1: 8-11.
 28. Larsson P et al. Oral bioavailability of clonidine in children. *Pediatr Anesth* 2011; 3: 335-340.
 29. Mikawa K et al. Efficacy of oral clonidine premedication in children. *Anesthesiology* 1993; 5: 926-931.
 30. Mikawa K et al. Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; 11: 977-981.
 31. Gulhas N et al. Oral clonidine premedication does not reduce postoperative vomiting in children undergoing strabismus surgery. *Acta Anaesthesiol Scand* 2003; 1: 90-93.
 32. Levinson M, Johnson C. Stability of an extemporaneously compounded clonidine hydrochloride oral liquid. *Am J Health Syst Pharm* 1992; 1: 122-125.
 33. Mikawa K et al. Oral clonidine premedication reduces postoperative pain in children. *Anesth Analg* 1996; 2: 225.

34. Tazeroualti N et al. Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. a prospective, randomized, controlled trial. *Br J Anaesth* 2007; 5: 667-71.
35. Pawlik MT et al. Clonidine premedication in patients with sleep apnea syndrome: A randomized, double-blind, placebo-controlled study. *Anesth Analg* 2005; 5: 1374-1380.
36. Sumiya K et al. Sedation and plasma concentration of clonidine hydrochloride for pre-anesthetic medication in pediatric surgery. *Biol Pharm Bull* 2003; 4: 421-423.
37. Homma M et al. Assessment of clonidine orally disintegrating tablet for pre-anesthetic medication in pediatric surgery. *Biol Pharm Bull* 2006; 2: 321-323.
38. Cunningham FE et al. Comparative pharmacokinetics of oral versus sublingual clonidine. *J Clin Anesth* 1994; 5: 430-433.
39. Gilkeson G, Delaney R. Effectiveness of sublingual clonidine in patients unable to take oral medication. *Drug Intell Clin Pharm* 1987; 3: 262-263.
40. Sarisuta N et al. Effects of surfactant on release characteristics of clonidine hydrochloride from ethylcellulose film. *Drug Dev Ind Pharm* 1999; 3: 373-377.
41. Bergendahl HT et al. Neuropeptide Y response to tracheal intubation in anaesthetized children: effects of clonidine vs midazolam as premedication. *Br J Anaesth* 1999; 3: 391-394.
42. Bergendahl H et al. Clonidine vs. midazolam as premedication in children undergoing adeno-tonsillectomy: A prospective, randomized, controlled clinical trial. *Acta Anaesthesiol Scand* 2004; 10: 1292-1300.
43. Lönnqvist P et al. Pharmacokinetics of clonidine after rectal administration in children. *Anesthesiology* 1994; 5: 1097-1101.
44. Johnston R et al. The use of rectal clonidine in the perioperative period. *Anesthesiology* 1986; 2: 288-290.
45. Larsson P et al. Onset time for pharmacologic premedication with clonidine as a nasal aerosol: a double-blind, placebo-controlled, randomized trial. *Pediatr Anesth* 2012; 9: 877-883.
46. Mitra S et al. Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial. *Indian Pediatr* 2014; 2: 113-118.
47. Almenrader N et al. Absorption pharmacokinetics of clonidine nasal drops in children. *Pediatr Anesth* 2009; 3: 257-261.
48. Babhair S et al. Comparison of intravenous and nasal bioavailability of clonidine in rodents. *Res Commun Chem Pathol Pharmacol* 1990; 2: 241-248.
49. O'connell F et al. Effect of clonidine on induced cough and bronchoconstriction in guinea pigs and healthy humans. *J Appl Physiol* 1994; 3: 1082-1087.
50. Lindgren BR et al. The effect of inhaled clonidine in patients with asthma. *Am Rev Respir Dis* 1986; 2: 266-269.
51. Nishina K et al. Clonidine in paediatric anaesthesia. *Pediatr Anesth* 1999; 3: 187-202.
52. Standing JF, Tuleu C. Paediatric formulations—Getting to the heart of the problem. *Int J Pharm* 2005; 1–2: 56-66.
53. Ivanovska V et al. Pediatric drug formulations: a review of challenges and progress. *Pediatrics* 2014; 2: 361-372.
54. Lopez FL et al. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. *Expert Opin Drug Deliv* 2015; 11: 1727-1740.
55. Spomer N et al. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Child* 2012; 3: 283-286.
56. Klingmann V et al. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. *J Pediatr* 2013; 6: 1728-1732.
57. Van Riet-Nales DA et al. Acceptability of different oral formulations in infants and preschool children. *Arch Dis Child* 2013; 9: 725-731.

58. Klingmann V et al. Acceptability of uncoated mini-tablets in neonates - a randomized controlled trial. *J Pediatr* 2015; 4: 893-896.
59. Romano MJ, Dinh A. A 1000-fold overdose of clonidine caused by a compounding error in a 5-year-old child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; 2: 471-472.
60. Ramesh V et al. Comparative study of oral clonidine and diazepam as premedicants in children. *Int J Clin Pharm Th* 1997; 5: 218-221.
61. Lam JKW et al. Oral transmucosal drug delivery for pediatric use. *Adv Drug Deliv Rev* 2014; 0: 50-62.
62. Patel VF et al. Advances in oral transmucosal drug delivery. *J Control Release* 2011; 2: 106-116.
63. Jannin V et al. Rectal route in the 21st Century to treat children. *Adv Drug Deliv Rev* 2014; 0: 34-49.
64. Hinton RL et al. Caregivers' acceptance of using artesunate suppositories for treating childhood malaria in Papua New Guinea. *Am J Trop Med Hyg* 2007; 4: 634-640.
65. Sam-Wobo SO et al. Rectal artesunates, their utilization, and parental perception in the management of malaria in children from Abeokuta, southwestern Nigeria. *Vector Borne Zoonotic Dis* 2012; 2: 151-155.
66. Lönnqvist P, Bergendahl H. Pharmacokinetics and haemodynamic response after an intravenous bolus injection of clonidine in children. *Pediatr Anesth* 1993; 6: 359-364.
67. Delgado-Charro MB, Guy RH. Effective use of transdermal drug delivery in children. *Adv Drug Deliv Rev* 2014: 63-82.
68. Hunt RD et al. Clonidine in child and adolescent psychiatry. *J Child Adolesc Psychopharmacol* 1990; 1: 87-102.

Table 1 Summary of the characteristics of different clonidine dosage forms. IV formulations were not investigated in this literature search, but an overview is presented here for reference.

	IV	Oral tablet	Oral liquid	Oral transmucosal	Rectal	Intranasal	Pulmonary
References	[9; 10]	[11-20]	[21-35]	[36-40]	[41-44]	[21; 22; 45-48]	[49; 50]
Ease of administration in PICU setting	+++	+	++	+	++	++	++
Typical child dose	0-3 µg/kg/h	4 mcg/kg	2-4 mcg/kg	2-4 mcg/kg	2.5 mcg/kg	3-4 µg/kg	150 mcg (adult)
Approximate onset of action (minutes)	10	120	90	120	45	> 30 (conflicting data)	
Cost of manufacture and development	+	+	+	++	+	++	++
Dose individualisation & flexibility	+++	+	++	+	++	+	++
Clinical/technical considerations	Painful, difficult in neonates	Requires ability to swallow solid dosage forms	Suitable taste masking vehicle required. Patient must be conscious to swallow liquid	Difficulty in dose adaptation and dose control	Unpredictable bioavailability	Variability of absorption Volume for delivery depends on device	Systemic effect of inhaled clonidine on sedation are currently not known
+ = low , ++ = medium +++ = high							

Table 2 Summary of clonidine source and vehicles used in liquid formulations.

<i>Clonidine source</i>	<i>Reference</i>
Crushed tablets	[26; 27; 32]
Catapresan injection	[21; 25]
Clonidine HCl powder	[28]
Source not specified	[22; 24; 29-31; 33-35]
<i>Vehicle/sweetener</i>	
Honey	[26; 27]
Apple juice	[24; 28-31; 33]
Simple Syrup	[32; 34]
Commercial ibuprofen suspension	[21; 25]

Table 3 Summary of oral transmucosal clonidine lollipop, orodispersible tablet (ODT) and sublingual tablet formulations.

<i>Study</i>	Sumiya et al. [36]	Homma et al. [37]	Cunningham et al. [38]
<i>Clonidine formulation(s)</i>	Lollipop	Lollipop, ODT	Sublingual tablet
<i>Indication</i>	Premedication	Sedation	hypertension
<i>Concentration</i>	2 or 4 mcg/kg	4 mcg/kg	0.3 mg
<i>Age</i>	1 to 11 years	1 to 11 years	20 to 42 years
<i>Number of subjects</i>	16	23	10
<i>Plasma concentration</i>	0.36±0.05ng/ml (2mcg/kg group) 0.50±0.16ng/ml (4mcg/kg group)	0.42±0.21ng/ml (lollipop) 0.75±0.15ng/ml (ODT)	1.3 ± 0.2 ng/ml (Cmax)
<i>Time of measured plasma concentration</i>	2 h	2 h	2.3 ± 1.9 h (Tmax)