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Rapid communication

Development and validation of a paediatric oral formulation of clonidine hydrochloride

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ABSTRACT

Many drugs are unavailable in suitable paediatric dosage forms. We describe the development and validation of a stable paediatric oral formulation of clonidine hydrochloride 50 μg/ml, allowing individualised paediatric dosing and easy administration. Stability of the extemporaneously compounded formulation of clonidine hydrochloride was assessed using a validated HPLC method. Clonidine hydrochloride was stable in the buffered aqueous solution at room temperature for up to 9 months. The described formulation is chemically stable for at least 9 months when stored in brown 100 ml PET bottles at room temperature, enabling adequate oral treatment in paediatric patients.

Oral liquids are broadly used in young children due to the need for flexible dosing and the danger of airway obstruction associated with swallowing solid dosage forms. However, limited liquid formulations are commercially available for paediatric use. In the Netherlands, a survey in 2005 of 6 large university hospitals showed the lack of standardisation in oral formulations and the absence of validated oral formulations for 45 drugs commonly used in children (personal communication member Dutch Special Interest Group paediatric pharmacy). Therefore, validated liquid dosage forms manufactured in hospital or community pharmacies are required to ensure accurate dosing and facilitate administration to children. This report describes the development and validation of a paediatric oral liquid formulation of clonidine hydrochloride (HCl) to cover the needs of paediatric patients. The chemical stability of the formulation was investigated for up to 9 months using a validated high pressure liquid chromatography (HPLC) method.

Clonidine is a partial agonist of the α_2-receptors. Its major pharmacological effects involve changes of blood pressure and heart rate and sedation (Westfall and Westfall, 2011). Clonidine is administered to adult patients for the treatment of hypertension, the prevention of menopausal symptoms and the prevention of symptoms of opioid withdrawal. It has efficacy in the off-label treatment of a variety of other disorders. In children, clonidine is mainly used as a sedative in combination with benzodiazepines and to prevent withdrawal symptoms after prolonged administration of sedative drugs in intensive care units (Arenas-Lopez et al., 2004). It is also used in the treatment of attention deficit hyperactivity disorder, tic disorders, withdrawal of benzodiazepines, alcohol or opioids, neonatal abstinence syndrome, growth hormone stimulation tests and as premedication for anaesthesia and surgery (Arenas-Lopez et al., 2004; Du et al., 2008; Hoder et al., 1984; Loche et al., 1993; Osborn et al., 2010).

The only commercially available oral formulation of clonidine is a tablet (minimum dosage 25 μg). The recommended therapeutic dosage of clonidine for children is often smaller than the commercially available tablets, especially when clonidine is used as a sedative drug or to prevent withdrawal symptoms. Furthermore, children younger than 7 years of age are not able to swallow tablets (Yeung and Wong, 2005). The availability of a liquid formulation of clonidine would thus facilitate administration, allow proper dose adjustments, and avoid the need to manipulation of the tablet. Levinson and Johnson have described formulation and stability of a clonidine HCl oral liquid suspension extemporaneously compounded from ground tablets (Levinson and Johnson, 1992). The major drawback of this formulation is that it needs to be shaken to ensure content uniformity because it is a suspension. Moreover, stability was reported for only 28 days when stored at 4 °C in amber glass bottles. As an alternative to an oral liquid, the parenteral form of clonidine (Catapresan®) can be administered

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Table 1
Stability of liquid oral formulation of clonidine HCl.

	Time				
	1 month	2 months	3 months	6 months	9 months
% of initial concentration remaining	95.1	100.7	96.5	97.4	101.9
pH	5.1	5.0	5.0	5.1	5.0
Actual initial concentration: 50.8 μg/ml; initial pH: 5.1					

orally. Both the ampoule and the tablet contain clonidine as the hydrochloride salt, therefore it can be assumed that clonidine HCl will be absorbed from the injection solution with a good oral bioavailability (70–100%) (Frisk-Holmberg et al., 1981). However, the oral suitability of the parenteral solution is limited by the lack of excipients to improve taste, smell and microbial stability and most importantly by its high concentration (150 μg/ml). This high concentration results in difficulties to administer an exact dose, as either dilution steps or the administration of small volumes are necessary for paediatric dosing.

We developed an aqueous formulation of clonidine HCl. The solution was sweetened with saccharose and further corrected for taste and smell with raspberry essence, preserved with the antimicrobial agent methylparaben and buffered (pH 5) with citric acid monohydrate and disodium hydrogen phosphate to ensure stability of methylparaben. Clonidine HCl and all excipients were purchased from Spruyt-hillen, label Bufa (IJsselstein, the Netherlands) which has been audited in 2011 by the Dutch Society of Hospital Pharmacists and was certified as a 'reliable supplier of raw materials and excipients for manufacturing and compounding'. For stability testing, one batch of 1000 ml clonidine HCl 50 μg/ml was compounded by dissolving 10.2 g of citric acid monohydrate and 18.3 g of disodium hydrogen phosphate in 500 ml of distilled water. Once the buffer components were dissolved, 50.0 mg of clonidine HCl was added and dissolved by continuous stirring. Afterwards 200 ml of saccharose syrup ('Sirupus Simplex' containing 630 mg of saccharose and 1 mg of methylparaben per g) was added and homogenised. Subsequently 10.6 g of methylparaben solution 15% (w/v) was added under continuous stirring, 500 mg of raspberry essence was added and the volume was made up to 1000 ml using distilled water. The resulting acidic solution had a pH of 5.0. The batch was aliquoted per 100 ml in brown polyethylene terephtalate (PET).

For the analysis of clonidine HCl an HPLC method was used. The components were separated using a Shimadzu LC20 system, on a 150 mm × 4.6 mm C_{18} ODS-3 5 μm analytical column with a mixture of acetonitrile and ammonium acetate solution (10 mM, pH 7.8 ± 0.04 adjusted with 1 M potassium hydroxide) in the ratio 45:55 (v/v) as mobile phase, at a flow rate of 1.0 mL/min. Column temperature was kept at 40 ± 0.1 °C and UV detection was performed at 230 nm using a Shimadzu M20A diode array detector. The injection volume was 10 μl. This HPLC method was validated for linearity (n = 30, 6 replicates of 5 concentrations) over the concentration range of 7.5–12.5 mg/l, exhibiting a correlation coefficient of >0.999 and an insignificant F-value (p = 0.05) for 6 replicates of 5 quality control standards prepared with clonidine HCl p.a. (Sigma–Aldrich). Specificity was found to be 100% and precision was confirmed by coefficients of variation of 0.2% and 0.3% for repeatability (n = 6) and reproducibility (n = 12), respectively. Accuracy of the method was satisfactory with a recovery (n = 6) of 101.3 ± 1.3%. Samples of the compounded clonidine HCl solution were diluted 5 times with distilled water and quantified on a calibration curve (8.0–12.0 mg/l) of freshly prepared aqueous standard solutions of clonidine HCl p.a. using the validated HPLC method. All twofold sample analyses were preceded by a system suitability test (n = 5), complying with the requirements of a coefficient of variation ≤2.0% and capacity and tailing factors of >1.0 and <2.0, respectively.

During the long-term stability testing program, samples of the clonidine HCl solution are stored at room temperature protected from light. At the initial time point and after 1, 2, 3, 6 and 9 months, samples were tested for clonidine HCl concentration and pH and results are shown in Table 1. Clonidine HCl concentrations were stable over the 9 months period tested. The pH remained constant (5.0 ± 0.1). Additionally, the concentration of methylparaben was tested by a HPLC-UV method discriminating between methylparaben and 4-hydroxybenzoic acid. Methylparaben was shown to remain constant as its concentration was 100.1% of starting concentration 1.59 mg/ml after 11 months of storage, indicating no loss of adequate preservative concentrations. Microbiological testing was not performed as methylparaben has acceptable antimicrobial preservative efficacy in an aqueous solution buffered at pH 4.5–5.5 for samples kept at room temperature (Rowe et al., 2006). Ongoing stability testing is being performed and can possibly further prolong the shelf life of the product.

The taste of the formulation was evaluated on a small scale by two healthy human volunteers. They held approximately 1 ml of the solution in the centre of the tongue and considered the taste acceptable with bitterness lower than slight. Furthermore, we did not receive any complaints regarding the acceptability of the solution during regular clinical use in the paediatric ward.

In conclusion, the liquid formulation of clonidine HCl 50 μg/ml developed and validated at our hospital can be easily prepared by qualified professionals and is chemically stable for at least 9 months when stored in a brown 100 ml PET bottle at room temperature. This formulation without any excipients with potential toxicity in children enables flexible dosing and easy administration of clonidine HCl. Moreover, the standardised formulation may aid to explore the pharmacokinetic and pharmacodynamic parameters of oral clonidine HCl in paediatric patients.

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