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Formulation Optimization in a University Hospital: The Example of Pediatric Solutions of the ACE Inhibitor Captopril

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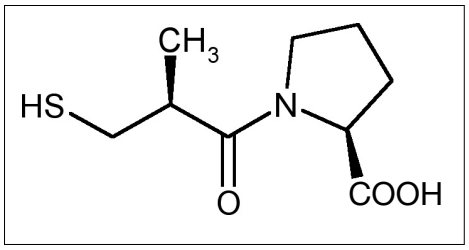
Abstract: Many major drugs are not available in pediatric form. As a result, hospital pharmacists are often requested to provide the medical staff with liquid formulations for individualized dosage and easy administration to newborn and young patients. Such in-house formulations must of course fulfil stringent criteria of purity and stability. This paper reports the development of a liquid solution of captopril for pediatric use. A specific HPLC-UV method was developed. A number of formulations described in the literature as affording one-month stability were examined and found wanting. A simple solution of the drug (1 mg/ml) in purified water containing 0.1% EDTA-Na proved chemically and microbiologically stable at room temperature for two years.

Keywords: Captopril · Chemical stability · Formulation · HPLC · Microbial stability · Pharmaceutical technology

1. Introduction

According to recent studies, a significant proportion of medicines prescribed to hospitalized children do not exist as a pediatric formulation [1]. This does not imply that the prescribed drug is uneffective or unsafe in children, but more simply that its producer had no incentive to develop such a form. Such a situation presents hospital pharmacists with a major challenge. Given the impossibility of administering tablets or capsules to newborns or infants, a liquid formulation has to be developed whose stability must be optimized and duration of validity assessed. The present paper describes such a study involving the oral formulation of captopril.



The structure of captopril

Captopril is a well-known inhibitor of angiotensin-converting enzyme (ACE) frequently used to treat arterial hypertension and congestive cardiac failure in adults and children [2][3]. Usual doses of captopril administered to premature and newborns range from 0.01 to 0.3 mg/kg 2–3 times per day.

Whereas the hydrolytic cleavage of captopril is negligible under pharmaceutically relevant conditions, its oxidative dimerization to a disulfide is a significant pharmaceutical problem. The reaction is catalysed by metal ions and its rate depends on pH and oxygen concentrations. Thus, the oxidation of captopril is lowest at pH 4, and is markedly slowed down by chelating agents, antioxidants, high concentrations of the drug, and a small and nitrogen-saturated headspace [4–7]. A number of studies have investigated the stability of captopril in a variety of oral vehicles, but none appears fully satisfactory [8–15]. The objective of our study was to obtain a captopril solution suitable for oral administration to newborns and young children and showing excellent chemical and microbiological stability.

2. Materials and Methods

European Pharmacopeia quality water obtained by reverse osmosis was used [16]. Captopril Pharm. Eur. (produced by BUFA B.V. Pharmaceuticals Products) was supplied by Dynapharm (Meyrin, Switzerland). All analytical solvents and reagents were of HPLC grade.

The concentration of captopril was measured by HPLC [10][11]. A Varian automated HPLC system with StarStation software was used, consisting of a 9012 pump, a Prostar 410 autosampler, a 9065 diode-array (DAD) detector, and a computer. The stationary phase was a Hamilton PRP-1 analytical column (150 × 4.1 mm, 5 μm particle size, 100 Å pore size) heated to 50 °C. The mobile phase was a 77:23 v/v mixture of phosphoric acid 0.01 M and acetonitrile. Samples were diluted 1:10 with phosphoric acid 0.01 M, and the injection volume was 20 μl. Flow rate was 1.0 ml/min, and measurements were made at 205 nm. The retention time of captopril was 3.0 min and it was well separated from its breakdown products. The full details and validation will be published elsewhere.

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Microbiological tests were carried out at the beginning and end of the long-term study according to the protocol of the European Pharmacopeia 4th Edition [17].

In preliminary experiments (to be published elsewhere), captopril was shown to be fully stable in the presence of EDTA after one month at 5 °C, whereas ascorbate or reducing sugars produced decreases ranging from 15 to 25%. As a result of such tests, a simple formulation containing 1 mg/ml captopril and 0.1% EDTA-Na in purified water (reverse osmosis) was selected as the most promising one. Three identical batches were prepared separately and stored one at room temperature (22 ± 2°C), another at 4 ± 1°C, and one at 40 ± 2°C. Three flasks were sampled three times for each determination in each batch (captopril content by HPLC, microbiological and organolectic tests, pH).

3. Results and Discussion

Organoleptic observations (visual and olfactory) did not reveal any noticeable change over the entire storage time. The pH in all preparations (3.33 ± 0.01) remained constant throughout. This value is considered to be in the optimal range for captopril conservation [6]. Furthermore, slightly acidic pH values such as these are well tolerated orally.

Captopril concentrations (Table) remained remarkably stable over the entire study at 4 °C and at room temperature. At 40 °C, a marginal drop was seen such that the concentration had decreased by a few percent to 95.8 ± 0.68 % after 12 months.

No microbial growth (aerobic, anaerobic or fungal) was detected during the study in any of the samples stored at 4 °C, 22 °C, and 40 °C. A number of factors may explain this favorable outcome, namely a) the microbiological purity of the water used, b) the acidity of the solution, and c) the known bacteriostatic effect of EDTA-Na [18].

4. Conclusion

The liquid formulation developed and validated here offers an outstanding chemical and microbiological stability (at least two years at room temperature). This can be explained by using purified water as solvent and mastering the major factors favoring captopril oxidation. The determining role of EDTA-Na is worth stressing, since it combines cation-chelating and bacteriostatic properties. In summary, we propose an oral formulation of captopril for pediatric use which can be prepared with ease by qualified professionals, is stable for at least two years at room temperature, and allows individualized dosage and easy administration even to newborn patients.

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Table. Stability of a pediatric oral solution of captopril (1 mg/ml) in purified water (reverse osmosis) containing 0.1% EDTA-Na [a)]

Time	Temperature of storage		
	4 ± 1 °C	22 ± 2 °C (room temperature)	40 ± 2 °C
	Percent of initial concentration remaining (± SD, n = 9)		
1 day	100.0 ± 0.9	100.0 ± 0.9	100.0 ± 0.9
7 days	100.6 ± 0.9	101.4 ± 0.7	100.7 ± 0.8
21 days	98.0 ± 0.8	97.6 ± 0.6	97.8 ± 0.6
2 months	103.4 ± 1.0	102.6 ± 0.6	102.6 ± 0.7
6 months	98.5 ± 0.2	99.3 ± 0.4	100.1 ± 0.2
12 months	102.7 ± 2.5	103.2 ± 0.9	95.8 ± 0.7
24 months	101.4 ± 0.6	100.6 ± 0.8	ND

[a]Full results will be published elsewhere; ND = not determined