Development of a hydrochlorothiazide 0.5 mg/ml oral solution for children

Y.Y. Li, D.J. Postma, H.W.G. Wagenaar
Royal Dutch Pharmacists Association (KNMP)
The Hague, The Netherlands
Contact: y.y.li@knmp.nl

Objectives

In The Netherlands there are no licensed medicines available with hydrochlorothiazide that are suitable for children. Lack of standardised formulations may lead to a variety of preparations with different quality and strengths. The objectives of this study were:

- Improving quality of hydrochlorothiazide preparations by developing a standardised formulation with a shelf life supported by stability studies.
- Preventing medication errors due to differences in formulations and concentrations within the hospital and at home after discharge.

Study Design

- Applying national standard procedures by the Special Interest Group on Paediatric Medicine of the Dutch Association of Hospital Pharmacists (NVZA) to assess the therapeutic rationale.
- Applying national standard procedures to design an oral solution forchildren.
- Developing and validating a stability indicating HPLC-method to establish shelf life.
- Stability testing for: oral solution with API from two different manufacturers, in two different containers (glass and plastic), at 25 °C protected from light, at t = 0, 3, 6 ,9, and 12 months.
- Designing a patient information lea‡et by following a national standard procedure/ format.
- Determine nationwide quality of hydrochlorothiazide oral liquid preparations pre- and post introduction of the standardised formulation.

Results

Therapeutic rationale

The therapeutic rationale for children was established by literature study following national procedures. Evidence was found for: hypertension, tubular dysfunctions and nefrogenic diabetes insipidus

Formulation

A formulation was developed in order to obtain a robust hydrochlorothiazide 0.5 mg/ml oral solution, optimized for solubility, stability and taste. Main focus points were:

- Acidity: set at pH = 2.5 in order to obtain a stable solution which was also palatable.
- Concentration: set at 0.5 mg/ml in order to obtain a clear solution. This was the highest possible concentration that was also easy for calculating dosage volumes.
- Concentration methyl parahydroxybenzoate: set at 0.077% instead of 0.15% to prevent methyl parahydroxybenzoate from crystallisation.

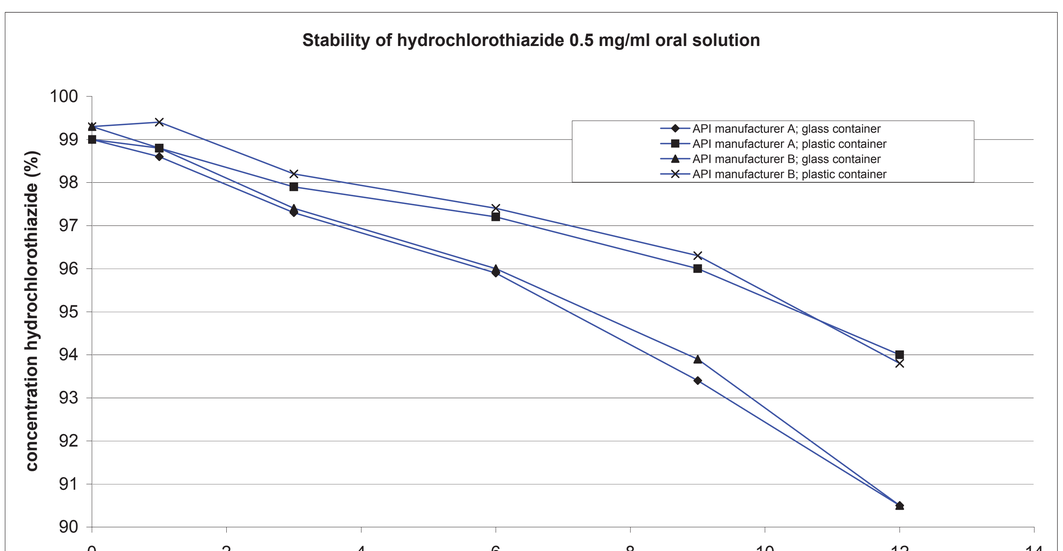
Formulation hydrochlorothiazide 0.5 mg/ml oral solution

Hydrochlorothiazide	50 mg
Citric acid monohydrate	870 mg
Disodium phosphate dodecahydrate	835 mg
Syrup*	32 g
Methyl parahydroxybenzoate	45 mg
Propylene glycol	275 mg
Orange essence	52 mg
Water	73.6 g
	107.7 mg (= 100 ml)

* Containing saccharose 63% m/v and methyl parahydroxybenzoate 0.1% m/v

Stability

- A validated stability indicating HPLC-method was developed, that was selective for salamide, parahydroxybenzoic acid and chlorothiazide.
- Presence of salamide was indicative of the presence of formaldehyde. The calculated amount of formaldehyde was considered to be safe.
- All tested variations of the oral solution (API-manufacturer and container remained stable (= 90-110% according to Dutch legislation for pharmacy preparations) during 12 months. Shelf life was set at t = 6 months to allow for variations in compounding.



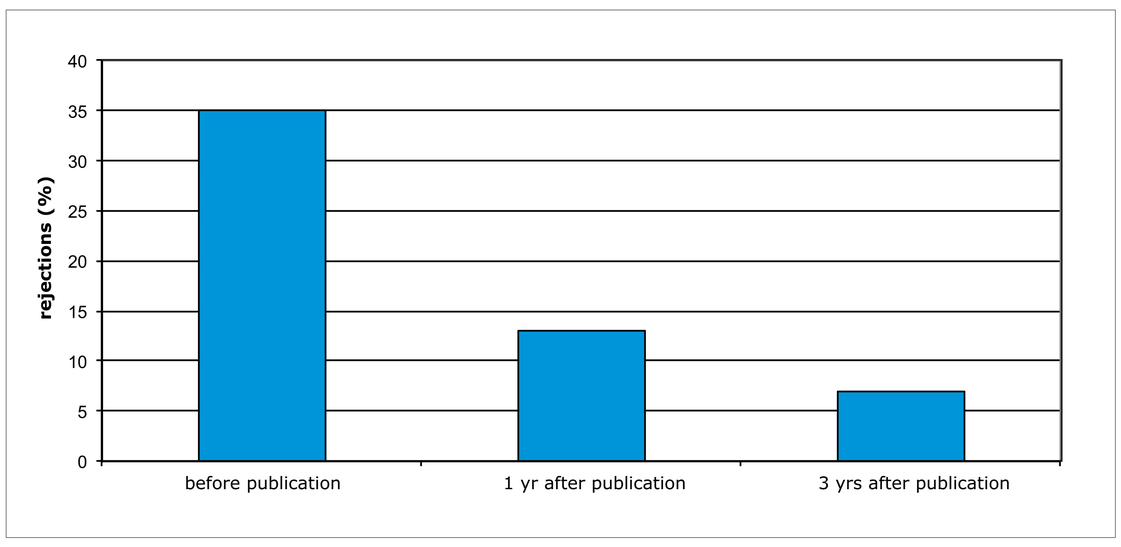
Patient information

A patient information lea‡et providing information on indication, use, precautions, interactions and storage was developed.

Overall quality

Quality of hydrochlorothiazide oral liquid preparations were centrally tested by our laboratory. Pharmacists nationwide were invited to submit samples of their own preparations. The amount of samples rejected due to formulation and compounding errors decreased 5-fold after introduction of a standardised formulation

Overall quality of hydrochlorothiazide oral solution before and after introduction of a standardised formulation



Conclusions

In The Netherlands a standardised formulation in the Formulary of Dutch Pharmacists (FNA) includes the assessment of therapeutic rationale and the development of a patient information lea‡et. A standardised formulation of hydrochlorothiazide 0.5 mg/ml oral solution was developed, with special consideration to stability, palatability, an easy manageable concentration for dosing purposes and a stable concentration of the preservative.This formulation proved to be stable for at least 6 months. Furthermore, after introducing the formulation, overall quality nationwide of hydrochlorothiazide oral liquid preparations improved greatly.

Acknowledgements

Special thanks to the Paediatrics Special Interest Group of the Dutch Hospital Pharmacists Association.