

PROJECT REVIEW

"Detection and stability of thiazide drugs"

F. Delbeke, K. Deventer (Doping Control Laboratory, University of Ghent, Belgium)

Diuretics are an indispensable group of therapeutics used to regulate the excretion of water and salts. By definition diuretics are drugs which increase the urinary flow. In sports diuretics are used for two main reasons: to flush previously taken prohibited substances with forced diuresis and in sports where weight classes are involved to achieve acute weight loss. Diuretics are banned in sport by WADA. Diuretics cover a wide range of chemical products and one important group of diuretics are the thiazides. Because thiazides cover a whole class of structure related compounds, only a few thiazides are mentioned by name in the prohibited list: i.e. bendroflumethiazide, chlorothiazide and hydrochlorothiazide.

Thiazides have an amidophenamide (AP) structure in common. AP is described as an aqueous degradation product for thiazides. Because of the potential hydrolysis of thiazides in urine this latter compound should be included in the screening methods for diuretics.

Because the information regarding the degradation is limited a study concerning the degradation parameters can provide new and useful insights for doping analysis. In this project the effect of pH and temperature will be investigated. Three thiazides will be included in this study: altizide, hydrochlorothiazide and chlorothiazide. Altizide and hydrochlorothiazide are commercially available on the Belgian market. Chlorothiazide was also included in this study because it can be detected as metabolite for hydrochlorothiazide and bemetizide.

Metabolites or degradation products can often be detected for a longer time in urine than the parent compounds. Therefore, in a second part of this project the detection times of metabolites and degradation products for two commercial available thiazide preparations, namely Docspirochlor (containing hydrochlorothiazide) and Aldactazine (containing Altizide), will be investigated.

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Results and Conclusions

The goal of this project was to investigate the stability of the thiazide diuretics altizide, hydrochlorothiazide and chlorothiazide both in vitro and in vivo. Not only the degradation of the parent drug was investigated also the formation of the degradation compound 4-amino-6-chloro-1,3-benzenedisulphonamide was monitored.

The results of the in vitro studies show that the thiazides are degraded faster at higher pH and higher temperature. In particular the lower pH improves the stability. When altizide and hydrochlorothiazide were exposed to UV-light, they photodegrade to chlorothiazide. When the degradation rate between the different compounds was compared for a given temperature and pH, altizide is the most unstable compound. Concentrations ranged between 41-239 ng/mL and 60-287 ng/mL after altizide and hydrochlorothiazide administration, respectively.

Publications

Deventer K, Baele G, Van Eenoo P, Pozo OJ, Delbeke FT. Stability of selected chlorinated thiazide diuretics. *J Pharm Biomed Anal.* (2009); 49(2):519-24.

Deventer K, Pozo OJ, Van Eenoo P, Delbeke FT. Detection of urinary markers for thiazide diuretics after oral administration of hydrochlorothiazide and altizide-relevance to doping control analysis. *J Chromatogr A.* (2009); 1216(12):2466-73.