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Interference of Metamizol (Dipyrone) on the Determination of Creatinine with the Kodak Dry Chemistry Slide Comparison with the Enzymatic Method from Boehringer

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Summary: In order to eliminate positive interferences that take place with the *Jaffé* technique, the Kodak Ektachem and Boehringer Mannheim Companies have chosen an enzymatic method for the determination of creatinine in serum and urine. Pathological and clinical samples often contain metabolites in elevated concentrations or exogenous compounds such as drugs or toxic compounds. We noticed that patients receiving metamizol-containing drugs showed unusually low values of creatinine when determined with an Ektachem analyser. We investigated the effect of the main metabolites of this prodrug on the creatinine enzymatic methods of Kodak and Boehringer. We concluded that methyl-amino-antipyrine, the active substance after administration of metamizol (prop. INN) was responsible for the interference, and that no reliable determination of creatinine could be performed with these methods in the serum of patients receiving this drug.

Introduction

Though registration of metamizol (dipyrone) has been cancelled in some countries (e. g. USA) due to rare cases of drug-induced agranulocytosis, this drug is a widely used analgesic in Switzerland and other European countries. The creatinine determinations of patients receiving "Novalgin®" gave surprisingly low values with the dry slide enzymatic method of Kodak Ektachem. This first observation was later confirmed by *Gascon* et al. (1). The other enzymatic method from Boehringer gave similar interferences.

In order to study drug interference in chemical tests, the in vivo relevant drug and/or metabolites at their respective concentration after usual dosage are to be considered.

The metabolism of metamizol has been extensively studied (2). It has been shown that after iv. or oral administration of the drug in healthy humans, the hydrolysed compound, methyl-amino-antipyrine, is mainly detected. Metamizol can thus be considered as a prodrug, methyl-amino-antipyrine being the active substance. A 1 g iv. administration of metamizol in man, rapidly gives the hydrolysis product, methyl-amino-antipyrine (serum c_{max} = 57 mg/l) which undergoes either oxidation to formyl-amino-antipyrine (c_{max} = 3 mg/l) or demethylation to amino-antipyrine (c_{max} = 3 mg/l). Amino-antipyrine is further metabolised to acetyl-amino-antipyrine (c_{max} = 3 mg/l) (3). Methyl-amino-antipyrine, formyl-amino-antipyrine, amino-antipyrine and acetyl-amino-antipyrine are present in the highest concentrations, and represent more than 70% of all the identified metabolites of metamizol in humans (4).

Materials and Methods

Samples and standards

4-Amino-antipyrine (*p*-amino-phenazone) and antipyrine were from Fluka AG (Buchs, Switzerland). Methyl-amino-antipyrine, acetyl-amino-antipyrine and formyl-amino-antipyrine were synthesised by Hoechst and kindly offered for this study. Portions of 90 µl of serum were spiked with 10 µl of solutions containing 500 mg/l of metamizol, methyl-amino-antipyrine or antipyrine, and 15 mg/l of formyl-amino-antipyrine, amino-