Investigations on the Potassium and Magnesium Retaining Activity of Acidic Triamterene Derivatives in Combination with Furosemide

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Zusammenfassung

In der vorliegenden Arbeit wurden die magnesium- und kaliumsparenden Eigenschaften von Triamterenderivaten mit einer Carbonsäurefunktion in der Seitenkette in Kombination mit Furosemid untersucht. Es konnte gezeigt werden, daß die nach alleiniger Applikation nur schwach kaliumsparenden sauren Verbindungen in Kombination mit Furosemid brauchbare Kaliumsparer darstellen. Andererseits konnte bei diesen Derivaten weder nach alleiniger Applikation noch in Kombination mit Furosemid ein antimagnesiuretischer Effekt beobachtet werden.

Summary

In this study the magnesium and potassium retaining properties of triamterene derivatives with a carboxylic acid moiety in the side chain were examined in combination with furosemide. It could be demonstrated that the acidic compounds with only weak potassium retaining effects when applied alone, are useful potassium sparing agents in combination with furosemide. On the other hand no magnesium retaining properties of these derivatives were found, even in the presence of furosemide.

Résumé

Dans la présente étude l'effet réducteur sur la magnésium et les potassium des dévirés triamtérènes a été analysé avec une fonction de l'acide carbonique sur la chaîne latérale en combinaison avec du furosémide. Ces études montrent que l'unique application d'une substances acide à faible réducteur de potassium avec du furosémide présentent des réducteurs de potassium utilisables. D'autre part on ne pouvait pas observer dans ces dérivés – ni aprés la seule application ni en combinaison avec du furosémide – un effet antimagnésiurétique.

Introduction

The increased potassium excretion caused by thiazide and loop diuretics can be prevented by a combination with the potassium sparing diuretic triamterene [10, 11].

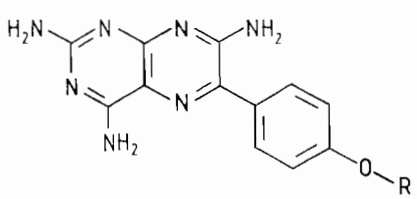
To avoid incompatibilities by the parenteral application of triamterene together with the acidic loop diuretic furosemide, acidic ether derivatives of 4'-hydroxytriamterene were synthesized [8]. Dose-response-investigations of 4-(4-Carboxybutoxy)triamterene (Sn1), a compound with a straight side chain, showed indeed potassium retaining properties [4], but the water-solubility of this derivative was not satisfactory [9]. On the other hand the branched side chain carboxylic acids 4-(1-Carboxy-1-methylethoxy)triamterene (Si1) and 4-(2-Carboxy-2-methylpropoxy)triamterene (Si2) showed a better solubility [6], but no antikaliuretic effect was found by dose-response investigations [4].

Early studies with triamterene analogues however, have shown that some derivatives possess antikaliuretic as well as antimagnesiuretic properties in experiments with white wistar rats [1]. A non-ionisable oxygen function (i.e. a hydroxy-, ether-, carbonyl- or carboxamide group) in the aliphatic or aromatic side chain of these triameterene derivatives was found to be responsible for their antimagnesiuretic effect [2, 3]. RPH 3048, a triamterene derivative with a sulfonamide side chain, also showed magnesium retaining properties [7].

On the other side, dose-response-investigations with triamterene carboxylic acid ethers revealed that compounds without any further oxygen function in the side chan have no magnesium retaining effect [3, 6].

In the present study the capability of acidic ethers of 4'-hydroxytriamterene to prevent kaliuretic and magnesiuretic effects caused by furosemide was investigated.

The structures of the tested compounds are shown in fig. 1.



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Sn 1 $-(CH_2)_4-COOH$

Si 1 $-C(CH_3)_2-COOH$

Si 2 $-CH_2-C(CH_3)_2-COOH$

Fig. 1: Structural formulas of the tested compounds and abbreviations used:
Sn1: 4-(4-Carboxybutoxy)triamterene
Si1: 4-(1-Carboxy-1-methylethoxy)triamterene
Si2: 4-(2-Carboxy-2-methylpropoxy)triamterene

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Material and Methods

The compounds were kindly supplied by Procter and Gamble Pharmaceuticals-Germany GmbH, Weiterstadt (Germany).

Male Wistar rats with a body-weight of 130–170 g were used for the experiments. They were kept in a climatized animal cage at 22 °C with a relative atmospheric humidity of 50%; the rats received a standard laboratory diet (Altromin®) and tap water ad libitum. Food was withdrawn 18 h prior to the experiment but access to water was unrestricted. The substances were dissolved in saline adding 0.1 N NaOH.

For each study, the animals (n = 6) were randomly divided into the treatment groups. Before intravenous application all rats received 20 ml/kg body weight of a 0.9% sodium chloride solution by gavage. Under light ether anaesthesia the test compound was injected in one of the caudal veins. 6 animals, serving as controls (C), were tested with the corresponding solvent only.

The rats were placed into individual metabolism cages without food and water. After a defined collecting period the urine volumes were measured and the concentrations of Na^+ and K^+ were determined by flame photometry, those of Mg^{2+} by atomic absorption using the Elektrolytautomat FL 6 (Zeiss, Oberkochen, Germany).

In the histograms, data were presented as means with standard errors of the mean (S.E.M.). Differences between mean values were tested for statistical significance by U-test of *Wilcoxon, Mann* and *Whitney* [5]. The differences between the findings were considered significant (*) at $p < 0.05$.

Results and Discussion

After a collecting period of 1.5 h neither the urine nor the sodium excretion of furosemide was influenced by the acidic derivatives Si1 and Sn1 (fig. 2). On the contrary the furosemide induced potassium excretion was markedly reduced by Si1 and Sn1 with the straight chain acid Sn1 being the more potent potassium sparing compound. The magnesium excretion – induced by furosemide – was not significantly reduced by the acidic derivatives.

A similar effect is shown in fig. 3. The urine and sodium excretion of furosemide was slightly increased by Sn1 after a collecting period of 1.5 h, whereas the potassium excretion was reduced by Si2 and Sn1. Again the branched chain compound Si2 had a weaker potassium sparing effect than the straight chain derivative Sn1. No significant decrease in the magnesium excretion of furosemide was recognized by both acids.

Regarding the obtained results the carboxylic acid Sn1 with a straight side chain shows distinct potassium sparing properties when combined with furosemide.

Although the acid Si1 given alone has approximately an antikaliuretic $ED_{50} >$ 150 µmol/kg [4], a potassium retaining effect together with furosemide could

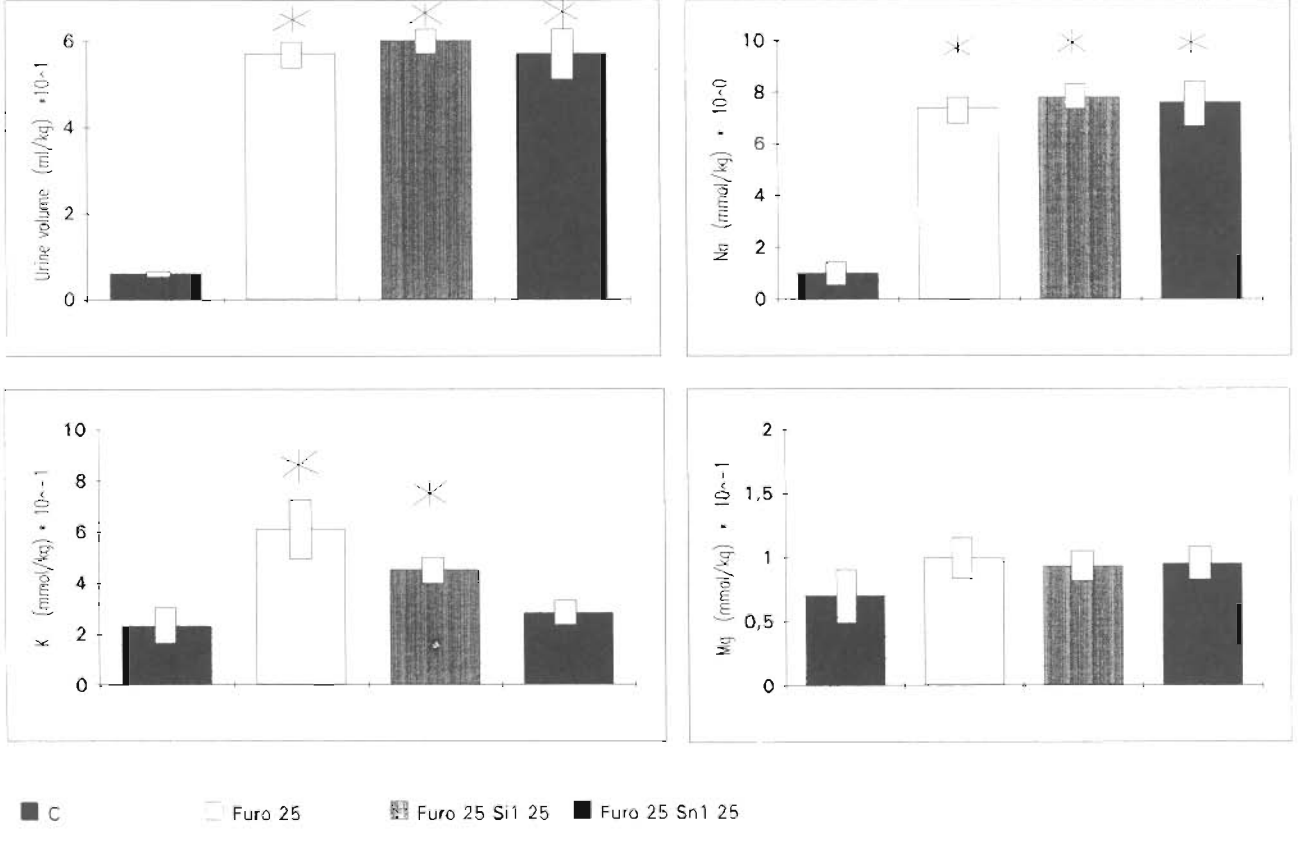

Fig. 2: Urine volume, sodium, potassium and magnesium excretion after i.v. application of 25 µmol/kg furosemide and combinations of 25 µmol/kg furosemide with 25 µmol/kg 4-(1-Carboxy-1-methylethoxy)triamterene (Si1) and 25 µmol/kg furosemide with 25 µmol/kg 4-(4-Carboxybutoxy)triamterene (Sn1) after a collecting period of 1.5 h.

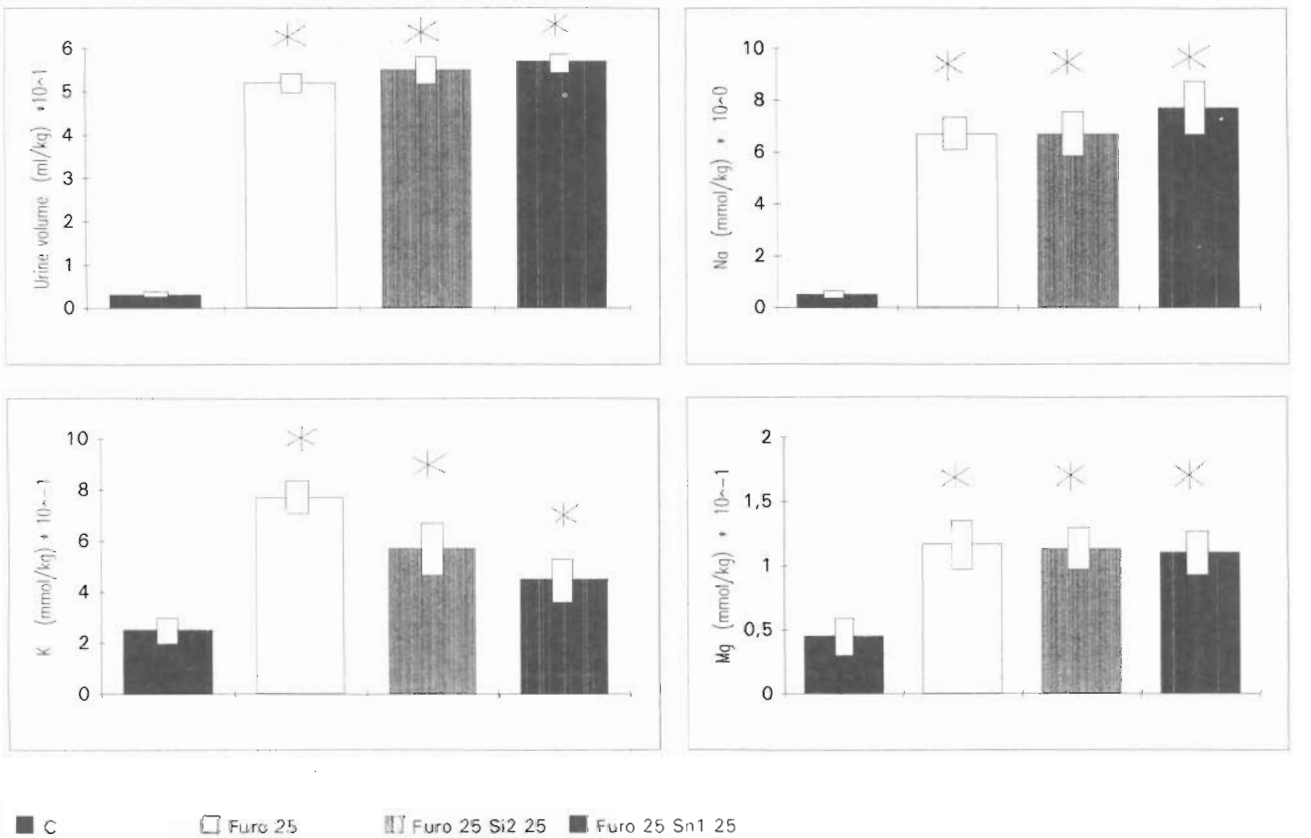

Fig. 3: Urine volume, sodium, potassium and magnesium excretion after i.v. application of 25 µmol/kg furosemide and combinations of 25 µmol/kg furosemide with 25 µmol/kg 4-(2-Carboxy-2-methylpropoxy)triamterene (Si2) and 25 µmol/kg furosemide with 25 µmol/kg 4-(4-Carboxybutoxy)triamterene (Sn1) after a collecting period of 1.5 h.

be reached with essential lower doses. The carboxylic acids Si1 as well as Si2 with branched side chains had lower antikaliuretic effects than the straight chain acidic derivative Sn1.

Furthermore the results substantiate that triamterene derivatives with only an acidic aliphatic side chain posses no magnesium sparing activities in combination with furosemide.

It seems therefore obvious that for the magnesium retaining activity a non-ionisable oxygen function with free pair of electrons for e.g. hydrogen bonding must be available [2, 3].

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