# Different Characteristics of Renal Excretion of Potassium and Magnesium after Application of Dimethylamino-hydroxypropoxytriamterene (RPH 2823) in Rats

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## Zusammenfassung

Mit der vorliegenden Arbeit wird ein weiterer Hinweis für die unterschiedlichen und voneinander unabhängig zu beeinflussenden Transportsysteme für $Na^+$, $K^+$ und $Mg^{2+}$ im spätdistalen Tubulus der Niere bei Ratten erbracht. Während RPH 2823 mit steigender Dosierung die renale $Na^+$-Ausscheidung stark erhöht, wird die Magnesiumexkretion dosisabhängig reduziert. Die Kaliumausscheidung wird bei niedriger Dosierung von RPH 2823 zwar ebenfalls verringert, steigt aber, im Gegensatz zur Magnesiurese, mit Zunahme der Dosis wieder deutlich an.

## Summary

In the present paper further evidence is provided that the transporting systems for $Na^+$, $K^+$ and $Mg^{2+}$ in the late distal tubule of the kidney in rats are different and can be influenced independently from each other. By elevating the dose, RPH 2823 causes a strong increase of the $Na^+$ excretion whereas the $Mg^{2+}$ excretion is reduced dose-dependently. In contrast to the effects on magnesium excretion the kaliuresis is decreased at low doses of RPH 2823 but reincreases significantly with higher doses.

## Résumé

Cet article apporte des preuves supplémentaires que les systèmes de transport de $Na^+$, $K^+$ et $Mg^{2+}$ dans le tube rénal distal tardif chez le rat sont différents et peuvent subir des influences indépendamment les uns des autres. Une élévation de la dose de RPH 2823 provoque une forte augmentation de l'excrétion de $Na^+$, alors que l'excrétion de $Mg^{2+}$ diminue de façon dose-dépendante. Contrairement aux effets sur l'excrétion du magnésium, la kaliurie est réduite aux faibles doses de RPH 2823, mais recommence à augmenter de façon significative aux doses plus élevées.


## Introduction

4-(3-dimethylamino-2-hydroxypropoxy) triamterene (RPH 2823) is an ether derivative of 4-hydroxytriamterene with a basic side-chain (fig. 1). It possesses potassium retaining as well as magnesium retaining properties [1].

The structural prerequisites for the magnesium retaining effect of triamterene derivatives were recently described [2, 3]. In the meantime pteridine derivatives have been found which have an antimagnesiuretic but no potassium retaining effect [5]. A model for the mode of action of triamterene derivatives with differentiated targets was proposed [6].

In the present paper the extent of renal excretion of $Na^+$, $K^+$ and $Mg^{2+}$ after application of RPH 2823 is described. The data provide further indication for different transporting systems of these ions in the late distal tubule of the kidney in rats which can be influenced independently from each other [6, 8].

## Material and Methods

RPH 2823 was kindly supplied by Procter and Gamble Pharmaceuticals-Germany GmbH, Weiterstadt/Germany.

Male Wistar rats with a body-weight of 130–170g were used for the experiments [7]. 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 R) and tap water ad libitum. Food was withdrawn 18h prior to the experiment but access to water was unrestricted.

The compound was dissolved in saline adding 0.1N HCl until pH 3 was reached.

For each study, the animals (n = 6) were randomly divided into the treatment groups. Before the intravenous application all rats received 20ml/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

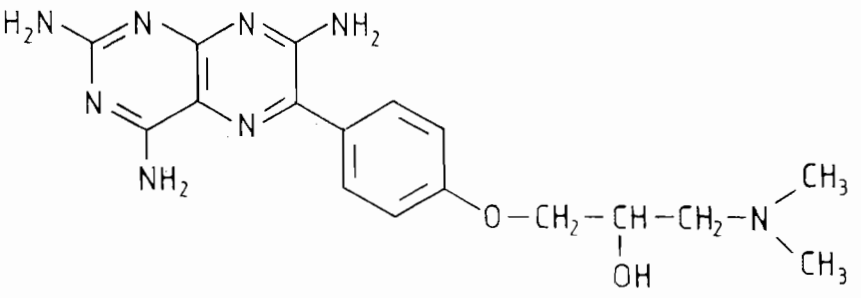


Fig. 1: Structural formula of 4-(3-dimethylamino-2-hydroxypropoxy) triamterene (RPH 2823).


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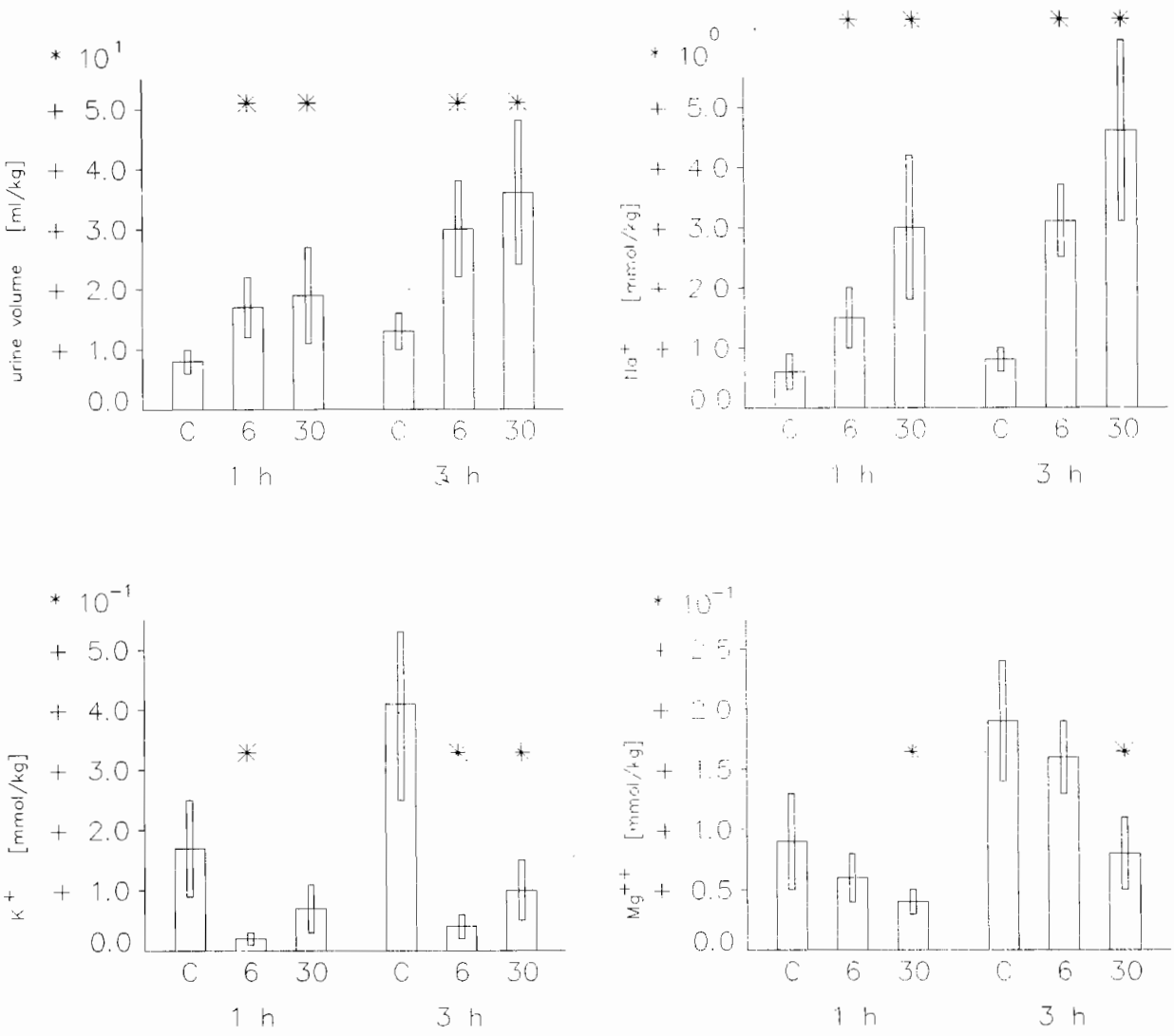


Fig. 2: Urine volume, sodium, potassium and magnesium excretion after intravenous application of 6$\mu$mol/kg and 30$\mu$mol/kg 4-(3-dimethylamino-2-hydroxypropoxy)triamterene (RPH 2823) and collecting periods of 1h and 3h (C: control).

treated 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 atom absorption using the Elektrolytautomat FL 6 (Zeiss, Oberkochen/Germany).
In the histograms, data are presented as means with standard error of the mean (S.E.M.). Differences between mean values were tested for statistical significance by U-test of *Wilcoxon, Mann* and *Whitney* [11]. The differences between the findings were considered significant (*) at $p < 0.05$.

## Results and Discussion

In fig. 2. the results after intravenous application of 6$\mu$mol/kg and 30$\mu$mol/kg bodyweight of 4-(3-dimethylamino-2-hydroxypropoxy)triamterene in conscious saline-loaded rats (collecting periods of 1h and 3h) are shown.
At a dose of 6$\mu$mol/kg of RPH 2823 the potassium excretion was strongly reduced accompanied by a simultaneous increased urine volume and sodium excretion after a 1h as well as after a 3h collecting period when compared to controls (C). The magnesium excretion was also decreased within both collecting periods. By raising up the dose of RPH 2823 to 30$\mu$mol/kg the urine volume and the sodium excretion furthermore increased, whereas the potassium excretion reincreased. In contrary, the magnesium excretion was significantly reduced within both collecting periods. These results indicate that in this model the maximum antikaliuretic activity of RPH 2823 is reached at 6$\mu$mol/kg, but the maximum antimagnesiuretic and natriuretic activity does not seem to be achieved at this dose. Since it is not possible to further increase the potassium retaining activity of RPH 2823 with higher doses, the increased amount of $Na^+$ causes an enhanced excretion of $K^+$ ions [7]. Hence in contrast to this effect the increased sodium excretion does not

lead to an increase of $Mg^{2+}$ excretion. The selective reincrease of potassium and decrease of magnesium excretion at a dose of 30$\mu$mol/kg RPH 2823 is not related to an antidiuretic effect, because such an effect is always characterized by a decrease of the total urine volume and electrolyte excretion [4, 7]. In addition, such an antidiuretic effect has not yet been observed in studies with triamterene derivatives containing a basic side-chain [7, 9].

Acute toxic effects may also not account for this effect since the $LD_{50}$ of RPH 2823 was calculated to be 59$\mu$mol/kg (95% confidence interval: 53–66$\mu$mol/kg). Moreover, the animals made an inconspicuous impression comparable to controls [10, 15].

A rebound effect is likewise not responsible for the increase of the potassium excretion at 30$\mu$mol/kg, too. Such an effect appears dose- and time-dependently [13], but is not expected after a 1h collecting period [9, 12, 14]. Therefore, at present the interpretation of the different characteristics of renal potassium and magnesium excretion after application of RPH 2823 is difficult. Further investigations are needed.

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