Pediatr Nephrol (2007) 22:144–148
DOI 10.1007/s00467-006-0293-1

BRIEF REPORT

# Prescription of drugs blocking the renin-angiotensin system in Italian children

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Received: 14 May 2006 / Revised: 17 July 2006 / Accepted: 20 July 2006 / Published online: 7 November 2006
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**Abstract** Little is known about the prescription pattern of antihypertensive drugs for children with impaired kidney function. We have therefore documented the use of antihypertensive drugs in this patient group by evaluating the Italian pediatric population-based registry of patients with chronic kidney disease on conservative treatment (ItalKid) from 1995 to 2003. In 1995, prescriptions written for antihypertensive drugs for use by children were approximately equally divided among drugs blocking the renin-angiotensin system and calcium channel blockers (38 vs. 43% of all prescriptions), followed by β-blockers and diuretics (15 and 4%, respectively). During subsequent years the proportion of prescriptions for drugs blocking the renin-angiotensin system increased (2003: 61%; $p<0.001$) and that of calcium channel blockers decreased (2003: 18%, $p<0.001$). In 1995, blockers of the renin-angiotensin

This research was carried out within the framework of the ItalKid Project and the CHI*ld* Project.

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system were prescribed, either as monotherapy or in combination, in 53% of the patients, but the relative frequency of the patients prescribed these drugs increased up to 83% in 2003 ($p<0.0005$). In conclusion, physicians caring for Italian children with impaired kidney function are increasingly prescribing drugs blocking the renin-angiotensin system.

**Keywords** Childhood · Hypertension · Kidney disease · Renal · Renin-angiotensin-system

## Introduction

Progression to end-stage kidney disease is largely due to factors unrelated to the initial disease including, among others, systemic hypertension [1]. In kidney disease the optimal therapy for hypertension has been largely empiric, since all classes of antihypertensive drugs have roughly equal efficacy on blood pressure [1]. However, it has become evident in recent years that in adult patients with chronic kidney disease, drugs that block the renin-angiotensin system are superior to a more conventional antihypertensive treatment regimen in preventing progression to end-stage kidney disease [2, 3]. Consequently, recent guidelines suggest that for children with chronic kidney disease the initial drug therapy for hypertension should be with agents that block the renin-angiotensin system, while other antihypertensive drugs can be added as necessary to achieve the treatment goals [1, 4]. In addition, agents that block the renin-angiotensin system can be used to slow the progression of kidney disease even in normotensive patients [1, 4].

Little information is available on the prescription pattern of antihypertensive drugs in children and adolescents with impaired kidney function [5, 6]. In the present study we document the prescribing pattern of antihypertensive drugs for Italian children with impaired kidney function.

## Patients and methods

The Italian pediatric population-based registry of patients with chronic kidney disease on conservative treatment (ItalKid) was established in 1990 [7–9]. The inclusion criteria are as follows: (1) a glomerular filtration rate (as calculated by the body height to plasma creatinine equations) of less than 90 ml/(min $\times$ 1.73 $m^2$), (2) less than 20 years of age at the time of registration and (3) conservative treatment. The follow-up continues after registration up to the beginning of renal replacement therapy. A form is sent to each of the participating centers every year in order to update the clinical and biochemical data for each subject. Collected data refer to the last visit before 31 December of each year. The ethics committee of the participating centers approved the design of the project and the submission of the corresponding data. The registry data from the years 1995, 1996, 1997, 1999, 2000, 2001, 2002 and 2003 were reviewed by searching for patients prescribed antihypertensive agents. The antihypertensive drugs were divided into following classes: drugs blocking the renin-angiotensin system (converting enzyme inhibitors or angiotensin II antagonists), β-blockers, calcium channel blockers, diuretics and other agents. The demographics of the patients enrolled in the Italkid project have been described elsewhere [7–9].

The two-tailed $\chi^2$-test with the Yates correction for continuity was used for analysis. A $p$ value below 0.05 was regarded as being statistically significant.

## Results

The registry data and the number of patients prescribed antihypertensive agents appear in Table 1. The relative frequency of patients prescribed antihypertensive drugs significantly increased ($p<0.001$) from 15% in 1995 to 24% in 2003.

**Table 1** Italian pediatric population-based registry of patients with chronic kidney disease on conservative treatment (ItalKid). Registry data for the years 1995 through to 2003 (no data were collected for the year 1998)

| Year | Number of patients | Patients treated with antihypertensive agents (%) | Prescribed antihypertensive agents | Mean number of antihypertensive agents prescribed per patient |
|---|---|---|---|---|
| 1995 | 685 | 104 (15) | 143 | 1.38 |
| 1996 | 839 | 116 (14) | 188 | 1.62 |
| 1997 | 749 | 118 (16) | 171 | 1.45 |
| 1999 | 709 | 137 (19) | 170 | 1.24 |
| 2000 | 717 | 183 (26) | 237 | 1.30 |
| 2001 | 644 | 189 (29) | 235 | 1.24 |
| 2002 | 523 | 163 (31) | 222 | 1.36 |
| 2003 | 522 | 127 (24)* | 214 | 1.68 |

*$p<0.001$ versus 1995

The data on the relative frequency of the prescribed antihypertensive agents (Fig. 1) indicates that in 1995 drugs inhibiting the renin-angiotensin system and calcium channel blockers were prescribed approximately equally (38 vs. 43% of the prescriptions), followed by β-blockers (15%) and diuretics (4%). In subsequent years the proportion of prescriptions for drugs blocking the renin-angiotensin system increased (2003: 61%; $p<0.001$), while that of calcium channel blockers decreased (2003: 17%; $p<0.001$). The frequency of β-blocker prescriptions showed a decreasing trend (2003: 9%; not significant), while that of diuretics showed an increasing one (2003: 9%; not significant). The increasing preference for drugs blocking the renin-angiotensin system is documented in the middle panel of Fig. 1. In 1995, drugs blocking the renin-angiotensin system were prescribed, either as monotherapy or in combination, in 53% of the patients, but the relative frequency of the patients prescribed these drugs significantly increased ($p<0.0005$) up to 83% in 2003. In both 1995 (69%) and 2003 (74%) the great majority of the patients were treated with a monotherapy, as depicted in the lower panel of Fig. 1.

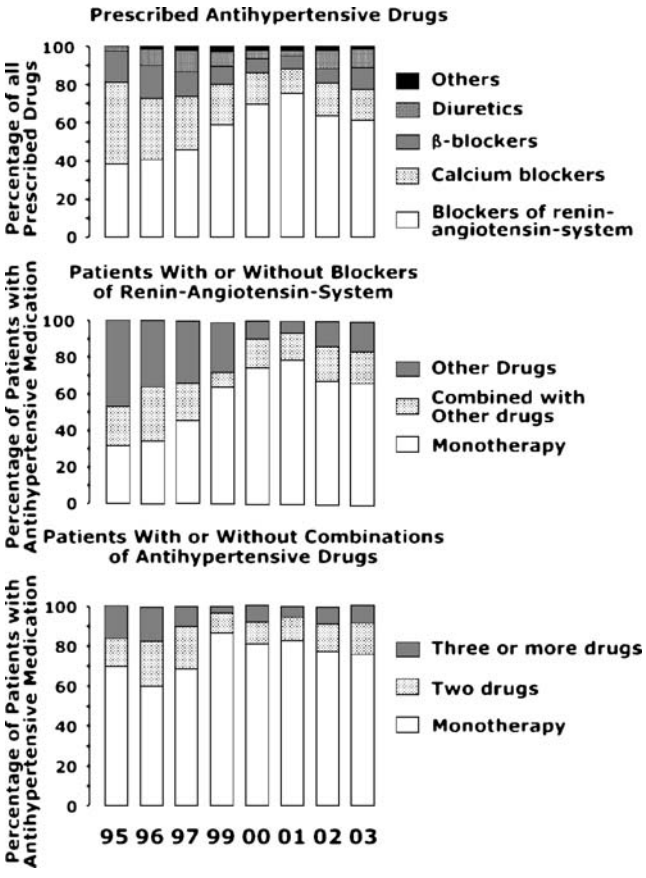


**Fig. 1** Antihypertensive medical treatment in Italian children and adolescents with chronic kidney disease. The *upper panel* depicts the prescribed classes of antihypertensive agents. In 1995, the frequency of prescriptions was fairly equal among drugs inhibiting the renin-angiotensin system and calcium channel blockers, followed by β-blockers and diuretics. In subsequent years the number of prescriptions written for drugs blocking the renin-angiotensin system increased ($p<0.001$), while that for calcium channel blockers decreased ($p<0.001$). The number of prescriptions written for β-blockers tended to decrease (not significant) and that for diuretics tended to increase (difference is not significant). The *middle panel* depicts the patients prescribed drugs blocking the renin-angiotensin system (alone or combination). In 1995, drugs blocking the renin-angiotensin system were prescribed for 53% of all patients. In subsequent years the relative frequency of the patients prescribed these drugs significantly ($p<0.0005$) increased. The *lower panel* depicts the relative frequency of patients treated with monotherapy, with two drugs or with three or more drugs against hypertension. In both 1995 and 2003 the great majority of the patients were treated with a monotherapy

## Discussion

For children and adolescents with kidney disease the prescription of antihypertensive drugs has been based more on individual experience than on recommendations from expert committees. Furthermore, considering that only limited data demonstrate the efficacy of renoprotection by drugs that block the renin-angiotensin system in children and adolescents [10–12], the preferential control of hypertension with a regimen containing either converting enzyme inhibitors or angiotensin II antagonists has not been generally recommended. This study assessed the prescribing pattern of antihypertensive drugs in children with impaired kidney function. The results indicate that physicians are increasingly prescribing drugs blocking the renin-angiotensin system for Italian children with impaired kidney function.

In this survey physicians caring for children with impaired kidney function rarely prescribed diuretics, as previously noted in North America [5]. Nonetheless, several authoritative bodies state that diuretics should be included in the antihypertensive drug regimen for chronic kidney disease [1, 2, 4]. The omission of diuretics from the therapy regimen likely reflects the fact that diuretics are sometimes inappropriate in tubulointerstitial diseases with salt wasting, which account for approximately 60% of all cases of impaired kidney function in Italian children [7].

The optimal blood pressure that will delay the progression of kidney disease during childhood is currently being estimated [12]. Nonetheless, the current recommendation is to lower blood pressure to lower-than-traditional goals [1, 4]. It has also been stated that single-drug therapy is unlikely to accomplish therapeutic goals in most hypertensive patients [1]. The present survey indicates, however, that in both 1995 and 2003 physicians caring for hypertensive children with impaired kidney function very rarely prescribed more than one antihypertensive drug.

This is the first nationwide study dealing with the pattern of prescribed antihypertensive drugs in children and

adolescents with impaired kidney function. The number of patients included in the registry was less in 2003 than in 1995, suggesting a diminished enthusiasm for complete reporting. The most recent data of the Italian registry are similar to those of a recent inquiry performed among North American pediatric kidney specialists [5], indicating that in the treatment of the hypertensive child with kidney disease and proteinuria, the most frequently used first-line agents are those that block the renin-angiotensin system (approximately 85%), followed by calcium channel blockers (approximately 15%). A very recent nationwide survey performed in Polish dialysis centers [6], however, indicates that in Poland physicians prescribe drugs blocking the renin-angiotensin system (approximately 50%) and calcium channel blockers (approximately 45%) fairly equally. The rationale underlying the fact that drugs blocking the renin-angiotensin system are only rarely prescribed in children with advanced kidney diseases is the high risk of severe, hazardous hyperkalemia in this setting [10–12].

The major limitation of the present study is the impossibility to assess whether blockers of the renin-angiotensin system were prescribed to treat hypertension or to slow the progression of kidney disease in normotensive subjects. This relates to the fact that the form sent every year to the participating centers does not specifically address this issue [7–9].

In conclusion, it is often assumed that guidelines based on the available evidence for the drug management of chronic kidney disease in adults do not have notable effects on prescribing patterns [13]. The present study indicates that physicians caring for Italian children with impaired kidney function are increasingly more often prescribing drugs blocking the renin-angiotensin system. Further research is needed to ascertain whether a more liberal combination with other agents should be encouraged.

**Acknowledgements** The ItalKid Project is supported by a research grant from the "Associazione per il Bambino Nefropatico". The present paper was written on behalf of all the members of the ItalKid Project whose contribution was essential.
G. Airoldi (Borgomanero), G. Amici (Ancona), A. Ammenti (Parma), B. Andretta (Padova), G. Ardissino (Milano), F. Ardito (Bologna), B. M. Assael (Verona), L. Avolio (Pavia), S. Bassi (Montichiari), F. Battaglino (Vicenza), R. Bellantuono (Bari), A. Bettinelli (Merate), C. Bigi (Lecco), S. Binda (Varese), D. Bissi (Gallarate), R. Boero (Torino), L. Bonaudo (Torino), M. Borzani (Milano), M. Bosio (Magenta), A.M. Bottelli (Varese), G. Bovio (Pavia), A.M. Bracone (Bra), G. Capasso (Napoli), M. Capizzi (Milano), D.A. Caringella (Bari), M.R. Caruso (Bergamo), D. Cattarelli (Brescia), M. Cecconi (Ancona), A. Ciofani (Pescara), A. Claris-Appiani (Milano), R. Coppo (Torino), R. Costanzo (Ragusa), P. Cussino (Savigliano), V. Daccò (Milano), M. D'Agostino (Bergamo), G. Daidone (Siracusa), R. Dall'Amico (Thiene), L. Dardanelli (Cuneo), R. De Castro (Bologna), M. De Gennaro (Roma), S. De Pascale (Bergamo), N. De Santo (Napoli), D. Delfino (R. Calabria), C.A. Dell'Agnola (Milano), L. Dello Strologo (Roma), F. Di Lorenzo (Bologna), P. Di Turi (Bologna), A. Edefonti (Milano), W. Erckert (Silandro), A. Fabris (Verona), V. Fanos (Verona), C. Fede (Messina), A. Fella (Napoli), R. Ferré (Breno), A. Ferretti (Napoli), P.A. Formentin (Cittadella), C. Fortini (Ferrara), E. Fossali (Milano), M. Gaido (Torino), L. Ghio (Milano), F. Giachino (Ivrea), M. Giani (Milano), S. Gianni (Siracusa), B. Gianoglio (Torino), P. Gianoli (Rivoli), M. Giordano (Bari), V. Goj (Milano), F. Grancini (Milano), G. Grott (Chieri), S. Guez (Milano), R. Gusmano (Genova), A. Iovino (Napoli), C. Isimbaldi (Lecco), A. La Manna (Napoli), G. Lama (Napoli), R. Landoni (Cinisello B.), S. Li Volti (Catania), A. Liardo (Caltagirone), V. Lotti (Cesena), R. Lubrano (Roma), N. Manganaro (Messina), M. Marangella (Torino), C. Marchesoni (Trento), S. Maringhini (Palermo), G. Marra (Milano), E. Marras (Torino), V. A. Mei (Bologna), N. Miglietti (Brescia), R. Mignani (Rimini), P. Minelli (Bologna), P.P. Molinari (Bologna), G. Montini (Padova), M. Montis (Cagliari), L. Murer (Padova), G. Nebbia (Milano), M. Neunhauserer (Brunico), M. Noto (Palermo), F. Paolillo (Lodi), T. Papalia (Cosenza), R. Parini (Milano), A. Passione (Foggia), L. Pavanello (Castelfranco V.), C. Pecoraro (Napoli), M.E. Pedron (Bolzano), I. Pela (Firenze), A. Pellegatta (Busto A.), P.N. Pelliccia (Chieti), M. Pennesi (Trieste), C. Pennetta (Manduria), R. Penza (Bari), L. Peratoner (Pordenone), F. Perfumo (Genova), G. Perino (Torino), C. Pesce (Vicenza), L. Pisanello (Padova), M. Pitter (Mirano), M.G. Porcellini (Torino), R. Prandini (Bologna), F. Puteo (Bari), I. Ratsch (Ancona), G. Riccipetitoni (Cosenza), G. Ripanti (Pesaro), N. Roberto (Milano), A. Rosini (Ancona), M. Rossi Doria (Bologna), S. Rota (Bergamo), M.L. Ruzza (Milano), D. Scorrano (Belluno), A. Selicorni (Milano), G. Selvaggio (Milano), F. Sereni (Milano), O. Sernia (Savigliano), C. Setzu (Cagliari), M. Tagliaferri (Treviglio), A. Turrisi (Trapani), S. Viola (Genova), G. Visconti (Palermo), A. Voghenzi (Ferrara), G. Zacchello (Padova).
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