Hyponatraemia and hyperkalaemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities

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Abstract

Background. This study was designed to examine the hypothesis that the nephrotoxicities caused by cyclosporin and tacrolimus might differ in respect of sodium and potassium handling.

Methods. 125 patients were studied retrospectively for the first 90 days after renal transplantation. Eighty were treated initially with cyclosporin and 45 with tacrolimus.

Results. A serum sodium level of $<135 \text{ mmol/l}$ was present for 542/5171 (10.5%) days under tacrolimus treatment compared with 377/5486 (6.9%) days under cyclosporin treatment ($P < 0.0001$). Severe hyponatraemia, below 120 mmol/l, was also more prevalent under tacrolimus than cyclosporin treatment, $P < 0.025$. Nine patients, all receiving tacrolimus, were treated with fludrocortisone for fluid depletion and/or hyponatraemia. Serum potassium levels were higher in tacrolimus-treated patients ($P < 0.0001$), and subjects with hyponatraemia were more likely to experience hyperkalaemia ($P < 0.0001$).

Conclusions. Hyponatraemia and hyperkalaemia were more frequent in tacrolimus-treated subjects. Taken together with previous work showing that hyperuricaemia is more frequent with cyclosporin treatment, and hypomagnesaemia with tacrolimus treatment, these findings are consistent with qualitative differences between the nephrotoxicities of cyclosporin and tacrolimus.

Keywords: cyclosporin; hyperkalaemia; hyponatraemia; kidney transplantation; nephrotoxicity; tacrolimus

Introduction

Although cyclosporin and tacrolimus both exert an immunosuppressive effect through inhibition of calcineurin-mediated immune responses, they differ from each other in respect of adverse effects. One difference is a small, but significant reduction of blood pressure in patients treated with tacrolimus, compared with cyclosporin. This has been reported in both randomized clinical trials and short-term clinical studies [1–4], and other studies that did not report a statistically significant difference have shown a trend in favour of tacrolimus [5,6]. It seems likely that this difference in blood pressure levels is related to differences in the nephrotoxicity of the two agents [1,3]. In our unit, an anecdotal impression was formed that the handling of salt and water in the first 3 months after transplantation differed in patients receiving either cyclosporin or tacrolimus. Therefore, this study examined blood pressure, diuretic requirement and serum sodium levels. Both cyclosporin and tacrolimus were used contemporaneously as primary induction therapy, according to the degree of HLA mismatch between donor and recipient. Therefore, the study was not entirely dependent upon historical controls to compare the effects of the agents.

Previous studies have shown that serum magnesium levels are lower in tacrolimus-treated than cyclosporin-treated subjects [2,5,7], and that serum urate levels are higher in cyclosporin-treated subjects than tacrolimus-treated subjects [8]. These abnormalities may be due to
differences in the renal tubular toxicity of these drugs. However, sodium and potassium levels have not been studied in detail previously.

Subjects and methods

A retrospective examination was made of 125 consecutive patients transplanted between July 1998 and May 2002. Routine immunosuppression was cyclosporin (Neoral), azathioprine and prednisolone until January 1999, after which patients with HLA-DR mismatched transplants received tacrolimus, azathioprine and prednisolone, and those with no donor–recipient HLA-DR mismatch continued to receive cyclosporin. Rejection was confirmed by biopsy and treated with 3 days of high-dose steroids. Severe or recurrent rejection was treated with conversion from cyclosporin to tacrolimus, or from azathioprine to mycophenolate mofetil if the patient was already taking tacrolimus.

Outcomes were measured according to ‘days at risk’ under treatment with either tacrolimus or cyclosporin, for the first 90 days after transplantation. This method was felt to account most fairly for patient and graft losses, for patients who converted from cyclosporin to tacrolimus, and also for patients who stopped calcineurin inhibitors completely. The numbers of days of hyponatraemia, and the number of days under treatment with sodium bicarbonate and fludrocortisone were recorded. Hypokalaemia was excluded if present on a sample taken immediately after a haemodialysis session.

If consecutive blood samples showed a biochemical abnormality, that abnormality was assumed to have been present throughout the period between the blood tests. Patients were seen three times a week in clinic for the first month after transplantation, and those with abnormal results were seen at intervals of no more than 7 days during the first 90 days after transplantation.

Anti-hypertensive medication was recorded by the number of ‘agent-days’ administered (e.g. if a patient received one agent for 60 days and a second for 50 days, a total of 110 ‘agent-days’ were recorded). Loop diuretic treatment was with frusemide in all cases. To take account of the dosage of frusemide administered, 40 mg was taken as a ‘standard dose treatment-day’ (e.g. for a subject who received 20 mg of frusemide for 20 days, 40 mg for 40 days and 80 mg daily for 20 days, 90 ‘standard dose treatment-days’ were recorded).

The blood pressure on day 90 after transplantation, or on the day in clinic closest to day 90, was recorded.

Biochemical analysis was performed on a multichannel autoanalyser (Modular System; Roche Diagnostics, Basel, Switzerland). The normal range for serum sodium was 135–145 mmol/l, measured using an indirect electrode method, and the normal range for serum potassium was 3.7–5.0 mmol/l. Statistical analysis was performed using Student’s t-test, chi-squared testing and Pearson’s correlation coefficient as appropriate.

Results

Baseline characteristics

Table 1 shows the characteristics of the study group. The differences between groups were expected, as tacrolimus was more likely to be administered to recipients of living-donor transplants, in whom the majority of transplants were HLA-DR mismatched. On the other hand, few of the cadaver donor transplants were HLA-DR mismatched. Seventy nine patients commenced treatment with cyclosporin and 46 with tacrolimus, and the Table 1 indicates the numbers of treatment crossovers and losses.

Hyponatraemia

Hyponatraemia was common. In the first 3 weeks after transplantation, 61/79 (77%) patients started on cyclosporin had at least one laboratory measurement of serum sodium below the lower limit of normal (135 mmol/l), compared with 27/46 (59%) started on tacrolimus (P = NS). From 21 to 90 days after the transplant, hyponatraemia was less common. Eighteen of 55 (33%) patients who continued cyclosporin experienced hyponatraemia, compared with 30/63 (60%) on tacrolimus (P = NS). Over the whole period, 63/79 (80%) patients who ever received cyclosporin experienced hyponatraemia, and 48/66 (73%) who ever received tacrolimus experienced hyponatraemia. At 90 days after the transplant, hyponatraemia was

Table 1. Characteristics of patients according to initial immunosuppressive therapy

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporin</th>
<th>Tacrolimus</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>79</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age (years)a</td>
<td>40.4 (1.3)</td>
<td>44.9 (1.6)</td>
<td>0.032</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>50</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Living-related transplants</td>
<td>6</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA-DR mismatch, zero mismatches</td>
<td>68</td>
<td>8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Died in the first 90 days</td>
<td>4 b</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Grafts lost in the first 90 days</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Converted to tacrolimus in the first 90 days</td>
<td>21 b</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute rejection in the first 90 days</td>
<td>28 (35%)</td>
<td>12 (26%)</td>
<td></td>
</tr>
</tbody>
</table>

aMean (SEM).

bTwo subjects were converted to tacrolimus before death, and another two who were converted to tacrolimus, discontinued tacrolimus as a result of haemolytic uraemic syndrome. Thus, at day 90, 54 subjects were receiving cyclosporin, and 60 tacrolimus.
uncommon, occurring in 3/53 (6%) patients receiving cyclosporin, and 4/51 (8%) receiving tacrolimus \((P = 0.0001\) and 0.0005, respectively). Although the sample size is small, this is consistent with a group difference independent of any direct effect of HLA-DR matching.

Table 2 shows the incidence of hyponatraemia and treatment with frusemide, anti-hypertensive drugs, sodium bicarbonate and fludrocortisone according to days at risk under treatment with cyclosporin and tacrolimus. Table 2 also shows that hyperkalaemia was more frequent during tacrolimus treatment and hypokalaemia during cyclosporin treatment. In order to eliminate, as far as possible, treatment differences between groups, Table 2 also shows results in only those patients who did not experience biopsy-proven rejection. Therefore, any confounding effects of high-dose steroid treatment and switching between drugs are eliminated. Differences with respect to serum sodium levels and serum potassium levels were maintained. Hyponatraemia may be consequent upon hyperglycaemia; however, hyponatraemia was seldom associated with hyperglycaemia in the patients studied here. There were 45 occasions in 17 patients where a laboratory measurement of blood glucose was made at the same time as the serum was <130 mmol/l; in only two of these cases was the blood sugar level >15 mmol/l, and the mean blood glucose was 7.9 (SEM 0.76) mmol/l.

Table 3 shows the blood pressures and number of anti-hypertensive drugs prescribed to patients receiving either cyclosporin or tacrolimus at 90 days after transplantation. These data, combined with the significantly lower exposure of tacrolimus-treated subjects to anti-hypertensive drugs shown in Table 2, indicate that tacrolimus was associated with less hypertension than was cyclosporin. The serum creatinine on days 10, 30 and 60 after transplantation was also recorded, and there were no significant differences between treatment groups [mean (SEM) \(\text{mmol/l}\), cyclosporin and tacrolimus, respectively: day 10, 233 (22.7) and 293.3 (38.2); day 30, 155 (12.1) and 187 (19.8); day 60, 139.7 (5.3) and 153.2 (8.2)].

Table 4 shows the incidence of hyponatraemia according to baseline differences between the tacrolimus and cyclosporin groups (shown in Table 1). Hyponatraemia was significantly more frequent under tacrolimus therapy amongst all the subgroups, apart from HLA-DR mismatched patients. There were only 12 patients who were started on cyclosporin after transplantation, all of whom were converted to tacrolimus for rejection. Therefore, our subsequent analysis was limited to these patients, with 32 days at risk under cyclosporin, 38 days at risk under tacrolimus, and 32 days at risk under cyclosporin and tacrolimus respectively. Day 15 (2.1%), and 36 (1.5%) at 18 (1.9%) and 36 (2.2%) respectively. \(P = 0.0001\) and 0.0005, respectively.)

Table 2. Outcomes according to cyclosporin or tacrolimus treatment

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporin (all patients)</th>
<th>Tacrolimus (all patients)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days/days at risk (%)</td>
<td>5486</td>
<td>5171</td>
<td>0.0209</td>
</tr>
<tr>
<td>Days with sodium &lt;120 mmol/l</td>
<td>1 (0.1%)</td>
<td>9 (0.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days with sodium &lt;125 mmol/l</td>
<td>13 (2.3%)</td>
<td>41 (0.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days with sodium &lt;130 mmol/l</td>
<td>68 (1.2%)</td>
<td>110 (2.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days with sodium &lt;135 mmol/l</td>
<td>377 (6.9%)</td>
<td>542 (10.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frusemide ‘standard dose treatment days’ administered</td>
<td>798 (1.45) (a)</td>
<td>465 (0.9) (b)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-hypertensive ‘agent-days’ administered</td>
<td>696 (1.27) (b)</td>
<td>5785 (1.11) (b)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium bicarbonate days administered</td>
<td>395 (7.2%)</td>
<td>1014 (19.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fludrocortisone days administered</td>
<td>0</td>
<td>417 (8.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days with potassium &gt;5.5 mmol/l</td>
<td>35 (0.6%)</td>
<td>77 (1.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium resonium days administered</td>
<td>109 (2.0%)</td>
<td>207 (40.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days with calcium &lt;3.5 mmol/l</td>
<td>164 (3.0%)</td>
<td>43 (0.8%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(a\)Standard dose treatment day = 40 mg of frusemide for 1 day.
\(b\)Mean dose per day.

\(\text{SEM} = \text{standard error of the mean}\)
Persistent hyponatraemia

To take account of hyponatraemia that may have been spurious or transient, patients who experienced <3 days of hyponatraemia were excluded and a subgroup analysis of persistent hyponatraemia performed. This strengthened the differences between the cyclosporin and tacrolimus groups; no patient on cyclosporin experienced a serum sodium of <120 mmol/l ($P = 0.0304$ compared with tacrolimus); for serum sodium <130 mmol/l, there were 37 days under cyclosporin treatment, and 91 days under tacrolimus treatment ($P < 0.0001$). None of the tacrolimus-treated patients in the persistent, <130 mmol/l group were receiving diuretics; six of them had excellent graft function [mean of serum creatinine levels simultaneous with hyponatraemia 150 (SEM 4.4) μmol/l]; two were recovering from delayed function, and one had progressive graft dysfunction.

Figure 1 shows that when patients who crossed over between therapies were excluded, although both drugs were associated with some early hyponatraemia, persistent hyponatraemia occurring more than 10 days after transplantation was almost solely associated with tacrolimus therapy, and that the prevalence of hyponatraemia was reducing by day 90.

Patients with persistent hyponatraemia on cyclosporin developed this within the first week after the transplant, and the mean levels of serum urea and creatinine on days when the serum sodium was <130 mmol/l were 24.1 (SEM 1.34) mmol/l and 579 (SEM 39.4) μmol/l, respectively. In the two patients who developed early hyponatraemia on tacrolimus, the mean serum urea and creatinine levels were 38.0 (SEM 2.8) mmol/l and 920 (SEM 84.7) μmol/l, respectively. In contrast, persistent hyponatraemia which started beyond the first 2 weeks was associated with reasonable graft function; the serum urea and creatinine levels were 12.8 (SEM 0.84) mmol/l and 204 (SEM 9.27) μmol/l, respectively, comparable with a mean serum creatinine of 187 (SEM 19.8) μmol/l in all tacrolimus-treated patients at day 30 after transplantation.

Urinary excretion of sodium and potassium

One hundred and four urine collections were obtained from 43 patients, 75 in patients taking tacrolimus and 29 in patients taking cyclosporin. The samples were collected between 10 and 218 days post-transplantation. Regression analysis showed that 24 h urinary sodium excretion was inversely associated with time after transplantation in tacrolimus-treated patients ($P = 0.016$), while there was no association between urinary sodium excretion and time after transplantation for cyclosporin-treated patients ($P = 0.55$). Table 5 shows the 24 h urinary sodium excretion and fractional excretion of sodium in the first 45 days after transplantation, compared with samples taken at later dates. This shows that sodium excretion in tacrolimus-treated subjects was higher in the first 45 days after transplantation than in samples collected later.

Urinary potassium excretion did not differ between treatment groups and was not associated with serum potassium levels. However, it should be noted that, in this steady state series, the there were only six cases with a serum potassium level of >5 mmol/l at the time of sample collection.
of the urine collection, with a highest serum potassium level of 5.4 mmol/l. Likewise, there were only six serum potassium levels <4 mmol/l, with a lowest of 3.4 mmol/l.

Differences between groups according to the presence of hyponatraemia

In order to detect any association between hyponatraemia and other clinical outcomes, subjects were divided into two groups according to whether a serum sodium level of <130 mmol/l had been experienced at any time during the first 90 days (n = 58), and those in whom serum sodium never fell below 130 mmol/l (n = 67).

Figure 2 shows the incidence of hyperkalaemia according to both hyponatraemia and drug therapy. Hyperkalaemia occurred most often not only under tacrolimus therapy, but in subjects who experienced serum sodium levels <130 mmol/l (P < 0.001).

Figure 3 shows the administration of anti-hypertensive drug therapy according to both hyponatraemia and drug therapy. Subjects receiving cyclosporin received more anti-hypertensive drugs, but this effect was most apparent in those who did not experience a serum sodium level of <130 mmol/l (P < 0.001).

Symptomatic hyponatraemia and use of fludrocortisone

Although hyponatraemia was usually asymptomatic, in a number of patients there was continued hospitalization for salt and water loss, and one patient experienced an acute encephalopathy. Renal failure was due to polycystic kidneys, and he was aged 45 years at the time of living-donor transplantation from his brother. One native kidney had been removed to achieve access for transplantation, and he had been receiving dialysis for 6 months. Serum sodium level had never been reduced during dialysis, or in the 7 years of nephrological review prior to the transplant. The serum creatinine fell to 124 μmol/l, and he was discharged from hospital on the ninth post-operative day with a serum sodium level of 140 mmol/l. He lost 7 kg in weight over 4 days at home, and was readmitted to hospital. After hydration with intravenous 0.9% sodium chloride he appeared to be stable and intravenous hydration was stopped. His serum sodium level fell from 130 to 116 mmol/l over 5 days, with accompanying weight loss and the development of an acute encephalopathy. He stabilized with intravenous 0.9% saline, fludrocortisone and sodium bicarbonate, but even with an oral fluid intake of >41/24 h required subsequent readmission to hospital for hydration. Twenty four hour urine collection, taken just after fludrocortisone was started, showed a volume of 4.47 l, and urinary sodium excretion of 347 mmol/24 h.

Nine patients, all receiving tacrolimus, were treated with fludrocortisone either for hyponatraemia or because excessive urine volume required hospitalization for intravenous fluid treatment. Fludrocortisone was not started in the first week after transplantation,
Hyponatraemia and tacrolimus

and the lowest plasma sodium level in the treated patients occurred at median 18 (range 14–79) days after transplantation. Seven of these had measurement of urinary sodium levels, median 78 (range 33–149) mmol/l, and 24 h excretion (five cases) median 273 (range 138–784) mmol/24 h. Fludrocortisone treatment seemed well tolerated, and was not associated with fluid overload or severe hypertension.

Discussion

The finding that hypertension was less severe in tacrolimus-treated subjects has been reported previously, and our results are consistent with published studies [1–4]. An increased incidence of hyponatraemia under tacrolimus therapy has not previously been reported, to our knowledge, in a large series of patients. A salt-losing nephropathy associated with tacrolimus was reported in isolated cases soon after the drug’s introduction into clinical use [9]. Hyponatraemia has been reported in recipients of combined pancreas and kidney transplants, but was attributed to sodium losses in exocrine secretions when the pancreatic duct was drained into the bladder [10].

Our findings may seem surprising because previous randomized trials comparing cyclosporin and tacrolimus did not report differences in the rates of hyponatraemia and hyperkalaemia [2,4,6,7]. In these trials, as in this study, the overall percentages of patients who experienced these abnormalities during the first 90 days did not differ according to drug therapy. However, we report significant differences in the severity and duration of the biochemical abnormalities, which the published randomized trials did not appear to be designed to detect.

A weakness of this retrospective study is that the treatment groups were not comparable at the time of transplantation. However, analysis was performed to take account of all the significant differences between the treatment groups. Excluding those who experienced acute rejection (Table 2), and analysing by subgroups to account of other differences between the groups at transplantation (Table 4), indicated that the differences in sodium and potassium levels were consistent in all subgroups. In addition, a control group of patients not receiving calcineurin inhibitors would have been desirable, but was not possible in our centre. Our data only indicate that the effects of the two drugs studied were different; it is uncertain whether cyclosporin might cause relative salt retention, or whether tacrolimus causes a salt losing nephropathy, or indeed both might occur. It is suggested that future randomized studies comparing immunosuppressive drugs in transplantation take account of the preliminary findings from this study to examine carefully the possibility of differences between the nephrotoxicities of drugs.

Hyponatraemia has a number of causes, which include tubular sodium wasting, relative water overload with dilution, or replacement of urine loss with intravenous fluid containing relatively less sodium in the early post-operative period [11]. It was felt that to attempt to judge between causes of hyponatraemia in a retrospective study of this type would introduce bias into the analysis. Therefore, all hyponatraemia in the study period was recorded, regardless of possible cause. It is important, though, to note that the cases of severe hyponatraemia, a plasma sodium < 120 mmol/l, did not occur in the immediate post-operative period when inappropriate intravenous solute replacement may cause hyponatraemia. Serious hyponatraemia did not occur during periods of delayed function, and was not associated with any excessive antacid consumption, hyperglycaemia or diuretic administration. The clinical picture of volume depletion, together with measurement of urine sodium losses in some of the subjects, confirms there was salt-losing nephropathy.

Fludrocortisone was more effective in our practice, anecdotally, than sodium bicarbonate for hyponatraemic patients receiving tacrolimus. Fludrocortisone has previously been used successfully to treat renal transplant patients with nephrotoxicity [10,12], and one previous report documented relative aldosterone deficiency [13]. There are also in vitro data indicating that cyclosporin and tacrolimus induce aldosterone resistance [14], and this effect may be greater with tacrolimus [15]. Aldosterone levels were not measured in the patients studied here.

Hyperkalaemia is a recognized complication of cyclosporin and tacrolimus, but has been examined carefully in only a few comparative studies. The mean potassium level was higher on tacrolimus than on cyclosporin in a study of eight renal transplant patients under treatment with each drug [16], and a trend toward more hyperkalaemia with tacrolimus was noted in a study of bone marrow transplant patients [17]. In the present study, hyperkalaemia was more frequent in tacrolimus-treated patients, in particular the subgroup who experienced a serum sodium level of < 130 mmol/l (Figure 2), suggesting the possibility of a common mechanism for the two phenomena.

The finding that hypokalaemia was more frequent under cyclosporin treatment was surprising. This effect was not due to potassium wasting under diuretic therapy. When all diuretic-treated subjects were excluded from the analysis, hypokalaemia occurred on 115/4836 days at risk under cyclosporin, compared with 41/4336 for tacrolimus (P < 0.0001). Hypokalaemia could be another manifestation of drug-induced nephrotoxicity, but further work would be necessary to confirm this.

The mechanisms of cyclosporin and tacrolimus nephrotoxicities are not fully understood, and there may be multiple mechanisms. Cyclosporin can cause abnormalities of glomerular filtration rate, proximal tubular function as assessed by lithium handling, and distal tubular function, evidenced by hyperkalaemia and acidosis [18]. In theory, all these abnormalities could be secondary to intra-renal vasoconstriction rather than direct renal tubular toxicity [1,3], but tacrolimus has less of an effect in this respect than cyclosporin, so that it would appear unlikely that
effects on renal blood flow only could explain the multiple biochemical abnormalities in tacrolimus-treated subjects.

Differences in distal renal tubular function, however, could explain the differences in sodium, potassium and magnesium levels observed in this and previous studies. One clinical study in renal transplant recipients showed that a distal renal tubular acidosis was more common in tacrolimus-treated than cyclosporin-treated subjects [16]. Cotransporter studies in the cultured renal distal tubular cell line MDCK have shown differences, in particular that tacrolimus increased the activity of the Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransporter, while cyclosporin reduced its activity [19,20].

In summary, renal transplant patients treated with tacrolimus experienced hyperkalaemia and hyponatraemia with greater severity and with greater duration than those treated with cyclosporin. These findings are consistent with differences between the nephrotoxicities of cyclosporin and tacrolimus which are consistent, at least partly, with the differences in renal tubular cell function and aldosterone resistance that have been described experimentally.

Conflict of interest statement. This study was performed without financial support. Our department has taken part in clinical trials supported by both Novartis and Fujisawa. In the last 5 years our unit has performed research sponsored by Novartis and Fujisawa, the companies who manufacture the drugs in this article.

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Received for publication: 24.4.03
Accepted in revised form: 31.8.03