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Practical pediatric nephrology

Practical aspects in the use of cyclosporin in paediatric nephrology

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Abstract. Many factors must be considered for the effective and safe use of cyclosporin A (CsA) in paediatric nephrology. Detailed knowledge of the variable bioavailability, tissue distribution, and metabolism, as well as causes which lead to their alteration are necessary. Factors which affect the activity of the mixed function oxidase system cytochrome P-450 must be considered, i.e. liver dysfunction and many drugs. Precise knowledge of the CsA determination method and the spectrum of metabolites is essential. In children with renal transplants, a body surface area-related dose will better meet the dose requirements than a body weight related-dose. For drug level monitoring whole blood rather than plasma should be used, and the parent drug level should be the main determinant; elevated metabolite levels may be important in suspected nephrotoxicity or liver dysfunction. Pharmacokinetic profiles are necessary to discover absorption problems or increased CsA clearance rates which necessitate shorter dosing intervals. In children with steroid-dependent minimal change nephrotic syndrome, remission without steroids is maintained as long as CsA is given. The appropriate starting dosage is 150 mg/m^2 per day; trough level monitoring is mandatory to prevent nephrotoxicity and to confirm adequate immunosuppressive drug levels which should be 80–160 ng/ml (parent drug level). Although the benefit of CsA has been reported in some cases of lupus erythematosus, its use should be restricted to severe cases only until its efficacy and safety has been confirmed in controlled trials.

Key words: Cyclosporin A – Absorption – Distribution – Metabolism – Monitoring – Clinical application

Introduction

Cyclosporin A (CsA) was first identified in 1972 by Borel et al. [1] of Sandoz Ltd. as a compound of the fungus *Tolypocladium inflatum*. Since then at least 25 natural cyclosporins have been isolated; only a few, namely CsA, C, D and M, have been found to exert strong in vivo immunosuppressive effects [2]. CsA – like the other cyclosporins – consists of a cyclic structure of 11 amino acids, 10 well known and 1 previously unknown [3].

CsA has been used in more than 100000 kidney transplantations all over the world [4]. Its use covers all areas of organ transplantation and many auto-immune diseases. In paediatric nephrology CsA is mainly used in kidney transplantation and nephrotic syndrome. There is also some evidence that CsA is effective in the treatment of systemic lupus erythematosus (SLE).

The pathophysiology of CsA was recently reviewed by Mason in this journal [5]. We will focus on practical aspects of the use of CsA giving essential pharmacological information on the absorption, distribution, metabolism, drug interactions and monitoring. The clinical application of CsA in kidney transplantation, in nephrotic syndrome and SLE will be discussed.

Absorption

The CsA molecule is hydrophobic and water insoluble, which causes the first problem in its clinical use. Large inter- and intrapatient variations in CsA absorption have been observed. The bioavailability (F) of CsA (i.e. the fraction of oral dose which reaches the central circulation intact) has been reported to be between 5% and 70%, with a mean of 30% [6]. The high variability is due to an incomplete absorption from the lumen of the upper intestinal tract; it is not due to a first-pass effect in the liver [7]. As is known from experience with liver transplantation, intact bile secretion is required for absorption and insufficient bile flow causes poor absorption.

For optimal and consistent absorption a proper mixture of the oral formulation (Sandimmun) with a drink is mandatory. Though not conclusively studied, chocolate milk seems to be the optimal vehicle for the dispersion; a mixture with apple juice is an alternative. Other drinks or

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changing the nature of the drinks may cause variable and lower absorption rates. Therefore, patients should continue to use the same drink for CsA dispersion.

In a controlled study it was shown that higher absorption rates could be obtained if CsA was given together with food [8]. This indicates that bile secretion, stimulated by meals, is an important factor for a better absorption and less variable bioavailability. Grevel [7] and Canafax et al. [9] speculated that circadian differences in CsA pharmacokinetics are likely to be caused by oral dosing without (a.m.) and with (p.m.) solid food. The oral dose of CsA required to achieve adequate CsA blood levels declines with time after transplantation. Grevel [7] reported a mean pre-transplant F of $38.6 \pm 17.6\%$ while post-transplant F increased to $49.3 \pm 24.2\%$ ($P = 0.03$). This amelioration may be due to improvement of uraemia-induced gastro-intestinal disturbances. Whitington et al. [10] postulated that the small bowel length is the chief determinant of the oral CsA dose required to achieve adequate blood levels. Hence explained the large dose requirements of CsA in small children.

The development of CsA capsules can be regarded as great progress in the oral application of CsA. Nashan et al. [11] demonstrated that pharmacokinetic profiles obtained with an oral solution and capsules were nearly identical. The advantage is that patients need no longer adhere to their dispersion solution, but can take the exact dose by capsule; this could help to reduce compliance problems in young adults. The main disadvantage for children are the fixed dosages of 25 mg or 100 mg/capsule, which make correct dosing difficult.

Distribution

CsA is widely distributed in many body tissues with highest concentrations in fat as expected from the lipophilic character [12]. The distribution volume varies between 3.5 and 13 l/kg body weight, in relation to body weight [13, 14]. CsA is found in liver, kidney, pancreas and adrenal glands in higher concentrations than in plasma, which seems to parallel the tissue content of the CsA-binding protein cyclophilin [15–17]. Low levels in the cerebral tissue are probably related to the inability of CsA to cross the blood-brain barrier. In blood, up to 70% of CsA is bound to erythrocytes, about 20% is found in plasma, and 5–20% is associated with lymphocytes [18]. As a consequence of CsA binding to blood cells, CsA levels measured in whole blood are always 1.5- to 3-fold higher than in plasma. Binding to erythrocytes is temperature dependent: lowering the temperature from 37°C to 21°C increases the uptake by red blood cells, leading to a fall of CsA concentrations in the plasma fraction [19, 20].

In the plasma fraction more than 80% is bound to proteins, mainly to lipoproteins. The major lipoprotein fractions involved are the high-density and low-density lipoproteins [21]. The biological relevance of this fraction, especially in patients with nephrotic syndrome, is unclear. Due to the high tissue-to-blood concentration ratio the relevance of CsA concentration monitoring in blood has been questioned. One should bear in mind that after discontinuing the drug high tissue concentrations may be detectable for months [7, 22, 23].

Metabolism

The metabolic clearance of the parent drug has been shown to be age dependent; it varies between 5.7 in adults and 11.8 ml/min per kg in children less than 10 years [24–26]. The mean elimination half-life in children is 7.3 h and it varies in adults between 10 and 27 h. CsA is extensively metabolized in the liver by the mono-oxygenase cytochrome P-450 in humans and animals [16]. A similar metabolic pattern has been described in kidney tissue and in whole blood [27]. About 24 metabolites resulting from biotransformation have been isolated from blood, from bile and urine. Metabolite 17 (hydroxylation on residue 1), metabolite 1 (hydroxylation on residue 9) and metabolite 21 (*N*-demethylation on residue 4) are considered as primary metabolites of CsA. Further oxidation of metabolite 1 and 17 generates metabolites 8, 10, and 16 (so-called secondary metabolites) [28, 29].

The biological significance of CsA metabolites is still controversial. Some authors reported that metabolite 1, 8, 17 and 21 were 10% less potent than unmetabolized CsA in a variety of immunosuppressive tests in vivo and in vitro [30–35], while others found in an in vitro mixed lymphocyte reaction that metabolite 1 and 17 were almost as immunosuppressive as CsA and metabolite 21 was about 50% as potent [36].

Ryffel et al. [37] showed that parenteral administration of metabolite 17 and a pool of metabolites extracted from human bile to rats caused no nephrotoxicity while a similar dose of CsA caused damage. The major route for the excretion of CsA is bile, i.e. more than 90%, whereas less than 6% is excreted in the urine [38]. Nephrotoxic episodes under CsA treatment were accompanied by an increase in unchanged CsA blood levels together with metabolite 17, or by an increase in circulating metabolites relative to unchanged CsA [39–41]. This suggested that CsA-associated nephrotoxicity can be attributed in part to metabolites. Wonigeit et al. [42] discussed two distinct patterns of blood level derangement associated with nephrotoxicity: the first one is associated with high parent drug levels, the second one is characterized by an increase in metabolite concentration resulting from severely disturbed CsA metabolite excretion with parent drug levels within the normal range. The ratio of monoclonal non-specific CsA level to monoclonal specific CsA level in the first type is normal (2.0 ± 0.2, parent drug level 400 ± 102 ng/ml), while it is highly elevated in the second type (10.3 ± 2.3, non-specific level 1321 ± 266 ng/ml). The incidence of the second type is rather low in patients with renal diseases and CsA treatment; and is anticipated only in those with severe liver dysfunction.

Drug interactions

Several comprehensive reviews on CsA-drug interactions have been recently published [43–46]. Different phar-

Table 1. Drug interactions with cyclosporin A (CsA)

Drugs increasing CsA levels	Drugs decreasing CsA levels	Drugs causing additive nephrotoxicity
Ketoconazole	Phenytoin	Amphotericin B
Erythromycin	Phenobarbital	Aminoglycosides
Josamycin	Carbamazepine	Ciprofloxacin
Norethisterone	Methylprednisolone	Trimethoprim
Danazol	Metamizole	Co-trimoxazole
Verapamil	Nafcillin	Melphalan
Diltiazem	Flucloxacillin	Colchicine
Nicardipine	Rifampicin	Aciclovir
Propafenon	Trimethoprin-	Non-steroidal anti-
Doxycycline	-sulphadimidine i. v.	inflammatory drugs
Frusemide		FK 506
Metoclopramide		
Cimetidine		

Nifedipine: potentiation of gingival hyperplasia
Lovastatin: myolysis or myopathy

i. v., Intravenously

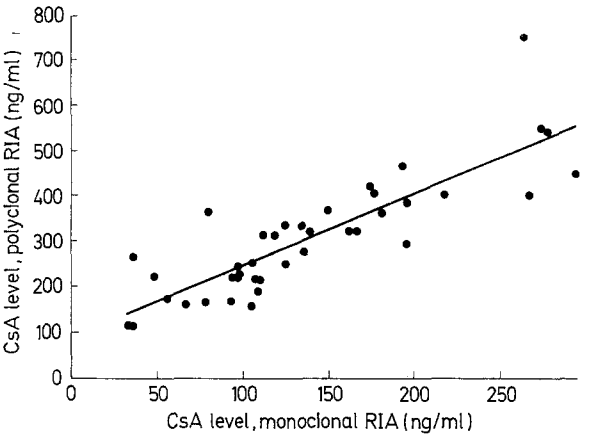

Fig. 1. Correlation between cyclosporin A (*CsA*) blood levels measured with the polyclonal antibody-based radio-immunoassay (*RIA*) and the monoclonal antibody-based RIA in children with renal transplants. CsA determination was performed with the Sandimmun kit; $n = 40$; $y = 1.58x + 88.7$; $r = 0.85$; $P < 0.001$

macological parameters are important sources of additional inter- and intra-individual variability of CsA. Drugs which affect gastro-intestinal motility, such as metoclopramide, can influence absorption, resulting in increased CsA levels. Phenytoin has been shown to reduce CsA absorption, although it was previously reported that its use increases the hepatic metabolism leading to decreased levels [47, 48].

Drugs which interfere with the cytochrome P-450 system must be used with caution. Stimulation of the activity of the cytochrome P-450 system increases the clearance of CsA leading to low trough levels. This is brought about by phenytoin, phenobarbital, carbamazepine, methylprednisolone, metamizole, nafcillin, flucloxycillin, rifampicin and trimethoprim/sulphadimidine intravenously [49–59]. Drugs with inhibitory effects on the cytochrome system decrease the clearance of CsA and lead to increased levels [60–75]: diltiazem, doxycycline, nicardipine, cimetidine, frusemide, norethisterone, danazol, propafenon, verapamil, ketoconazole and erythromycin. The last has also been shown to compete with CsA for metabolism [76].

Drugs with nephrotoxic potential could add to CsA nephrotoxicity. These are mainly the following: aminoglycoside antibiotics, amphotericin B, ciprofloxacin, colchicine, melphalan, trimethoprim and aciclovir [29, 43, 45, 77–79]. The cholesterol-lowering agent lovastatin has been reported in CsA-treated patients to cause severe myolysis, or a myopathy in approximately 30% [80]. The potent anti-hypertensive agent nifedipine has been reported to acelerate the degree of gingival hyperplasia caused by CsA, requiring operative gingivectomy in some cases [81]. Therefore, nifedipine should no longer be used in combination with CsA. The new immunosuppressive drug FK 506 aggravates pre-existing CsA nephrotoxicity if given together with CsA; therefore, co-administration should be avoided [82]. All drug interactions are summarized in Table 1.

Monitoring

Due to the variation in bioavailability and metabolism, and the possibility of various drug interactions monitoring of CsA blood levels is necessary. Which matrix should be used for the measurement of CsA? Since the binding of CsA to red blood cells is temperature dependent [83, 84], and there are difficulties in standardizing the separation of plasma or serum before measuring CsA, it is impossible to compare results from different centres. As a consequence the members of the Task Force on CSA Monitoring (requested by the American Association of Clinical Chemistry in 1985) recommended that whole blood should be the preferred matrix for CsA measurement [85].

Several assays have been developed to measure CsA levels. First, non-specific polyclonal antibody-based radioimmunoassay (RIA) was employed which allowed the measurement of unchanged CsA and a mixture of metabolites [86]. In 1987 a specific monoclonal antibody-based RIA became available offering the advantage of measuring the unmetabolized parent CsA alone [87]. In our experience the parent drug accounts for 40% of the levels measured by the polyclonal RIA in children with renal transplants (Fig. 1). The non-specific monoclonal antibody-based RIA allows the determination of the sum of parent CsA and almost all metabolites.

CsA determination by high-performance liquid chromatography (HPLC) was first reported by Niederberger et al. in 1980 [88]. This method has the advantage of detecting native CsA and most metabolites. However, the technical complexity of reliable HPLC measurement and the time consumption restricts this method to a few clinical laboratories [85]. The concentrations of the different metabolites measured by HPLC in children with transplants are shown in Fig. 2. A comparison of CsA levels measured by HPLC and monoclonal RIA revealed that they correlated well in the lower range, however, above a level of 200 ng/ml the levels corresponded less well (Fig. 3) (for a description of the HPLC method see [89]).

The so-called TDx methods (fluorescent polarization immunoassay) offer the advantage of short time measurement and a low coefficient of variation (CV). However, the polyclonal antibody used in this assay exhibited consider-

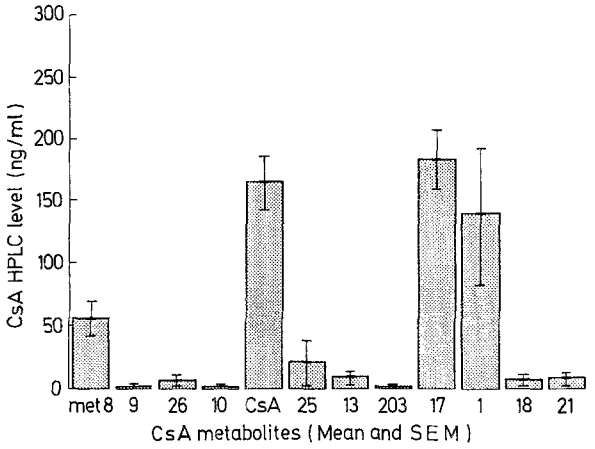

Fig. 2. Concentration of different CsA metabolites measured by high-performance liquid chromatography (*HPLC*). Measurements were done in 17 children at least 6 weeks after transplantation

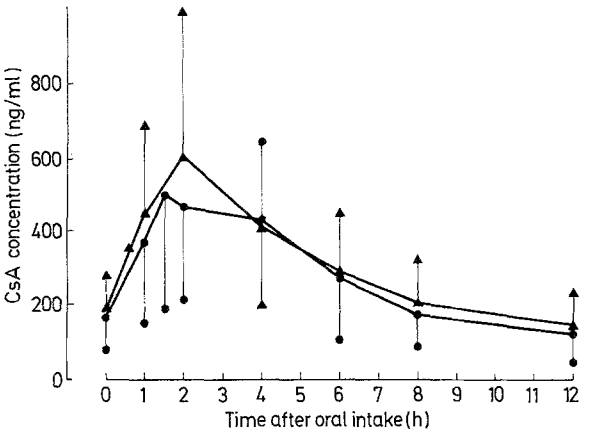

Fig. 4. Pharmacokinetic profile of CsA in 17 children more than 6 weeks after transplantation measured by HPLC (●) and monoclonal RIA (▲) (mean and SD)

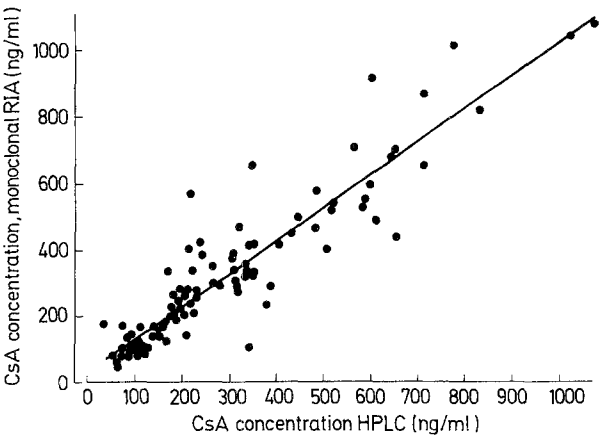

Fig. 3. Whole blood trough levels of CsA in children with transplants. Correlation between the monoclonal antibody-based RIA and the parent drug level measured by HPLC; $n = 104$; $y = 0.99x + 33.3$; $r = 0.93$; $P > 0.001$

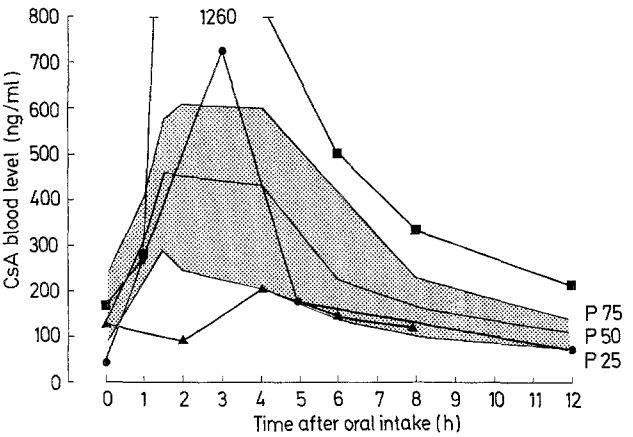

Fig. 5. Pharmacokinetic profile of CsA in three children who do not fit into the normal range of children with transplants (monoclonal RIA), depicted as shadowed area with the 25th–75th percentiles: Patient 1 (■) had an extremely high peak level despite an adequate zero level (12-h trough level before CsA intake) suggesting risk of nephrotoxicity. Lowering of the CsA dose resulted in a fall of serum creatinine concentration from 150 to 100 µmol/l. Patient 2 (●) (body weight 11 kg) started with a low zero level, had a relatively high peak and a rapid decrease demonstrating a high CsA clearance. As a consequence, CsA was administered 3 times a day. Patient 3 (▲) had a trough level in the desired range, however, a missing peak level suggested inadequate absorption. Three days after the profile, she developed a severe rejection episode and her CsA dose was increased

able cross-reactivity with CsA metabolites [90]. Recently, a monoclonal antibody for the TDx (Abbott Laboratories, Chicago, Ill.) has been developed. The TDx values were on average 24% higher than those obtained by HPLC with the same specimen ($y = 15.9+1.14x$, $r = 0.967$). The within- and between-run CVs are reported to be less than 2.5% and 5%, respectively [91], suggesting that this test could be superior to the RIA methods for future routine clinical use. The fact that TDx values may be higher should be considered when defining the therapeutic range. New methods like the Du Pont (Glasgow, England) aca (based on an affinity column-mediated immunoassay technology in which free and CsA-bound antibody-enzyme species are separated, followed by measurement of the enzyme beta-galactosidase) or the Emit from Syva (Palo Alto, USA) are under current clinical investigation [92, 93].

Until now, we have been using the monoclonal RIA routinely. However, the use of 12-h trough levels alone may be unsatisfactory if one has to monitor immunosuppression in children. In the case of low trough levels it is impossible to predict the reason. As outlined above, decreased bioavailability, increased metabolism due to the patient's age, or drug interaction may be the cause. Therefore, it is often necessary to measure a pharmacokinetic profile. Figure 4 presents the pharmacokinetic profile of children (mean age 12 years) in a steady state after transplantation. According to Grevel et al. [94] the area under the curve (AUC) correlates significantly with the oral dose ($r = 0.538$, $P = 0.0001$) in comparison with trough levels ($r = 0.136$, $P = 0.26$). He concluded that AUCs may better reflect the immunosuppressive and toxic effects of the administered dose than trough levels alone. We also use pharmacokinetic profiles in order to obtain the information about drug absorption and clearance. The clinical relevance of these profiles is demonstrated in three patients depicted in Fig. 5.

Clinical application

Renal transplantation

There is common agreement that after renal transplantation blood trough levels below 150 ng/ml (measured by monoclonal RIA) increase the risk of rejection, while levels above 250 ng/ml are accompanied by more pronounced nephrotoxicity. However, there may be an overlap between both situations; some individual patients may have signs of marked nephrotoxicity despite levels below 100 ng/ml, while others develop rejection with levels over 250 ng/ml. In treatment protocols using triple therapy, i.e. CsA, azathioprine and prednisolone, the therapeutic window for CsA levels can be lowered to 100–150 ng/ml, which is thought to decrease CsA nephrotoxicity. The 1989 report of the North American Pediatric Renal Transplant Cooperative Study [95] demonstrated that triple therapy is used in about 75% of children with renal transplants. With this immunosuppression, the current probability of 1-year graft function is 0.88 for living-related donor grafts and 0.71 for cadaveric grafts. However, the effect of azathioprine is difficult to estimate, and no pharmacological monitoring for azathioprine is available, which would allow an individual dosage adjustment. Currently, there are no controlled trials demonstrating that triple therapy is superior to CsA and prednisolone alone. Therefore, we routinely use only CsA with low-dose prednisolone. Azathioprine is added as an adjunct in cases of high immunological risk, i.e. third transplantation, high titres of cytotoxic antibodies or repeated rejection episodes, or in cases of initial non function as well as in cases with biopsy-proven CsA-associated nephrotoxicity with CsA levels in the therapeutic range [96].

Since a damaged kidney is more vulnerable to CsA, modern protocols delay CsA treatment until renal function has stabilized and cover this period with anti-lymphocyte antibodies. These protocols appear promising, and comparison of results from different centres have revealed lower creatinine levels in patients in whom the administration of CsA was delayed (patients who died or had graft loss were excluded [97]). However, some authors are concerned about the possibility of infectious complications [98] and the risk of developing malignancy [99].

We are convinced that optimal dosing and monitoring of CsA is essential for successful renal transplantation. Firstly the CsA dosage should be calculated on the basis of body surface area rather than body weight. This meets the dosage requirements better, since clearance rates are higher and elimination half times shorter in children than in adults [24, 26]. Our starting dose is 500 mg/m^2 [100] given in two divided doses. Dose adjustments are carried out in order to obtain blood trough levels (monoclonal RIA) in the range of 150–250 ng/ml during the first 2 months post transplant. Thereafter, levels between 100 and 200 ng/ml may be sufficient, depending on the individual immunological risk [96]. On an empirical basis we could demonstrate that the required CsA dosage per kilogram body weight correlated negatively with the total body weight, while the dosage per body surface area did not [101]. Therefore, with a uniform dosage based on body surface area we were able, in almost all cases, to achieve adequate blood trough levels early after transplantation [102]. Only children with a body weight of less than 10 kg, who had the highest clearance rate and shortest elimination half-life, were treated – dependent on their individual pharmacokinetic profile – with CsA at 8-h intervals [96]. Trough level monitoring should be carried out almost daily for the first 4 weeks, and later, dependent on the individual stability, twice or once a week. Mesurement of metabolites may give useful information if performed once a week for the 1st month, especially in patients with severe liver dysfunction. This enables metabolic disturbances and excess metabolites to be detected.

HPLC measurement of metabolites is currently used mainly in research but not in routine clinical practice. However, patients with problems of dose adjustment should have pharmacological profiles. The technique should also be used in patients with low trough levels despite adequate dosing, or in the case of suspected nephrotoxicity before the dosage is altered in large steps. Drugs which alter CsA metabolism or which cause additive nephrotoxicity should be used with caution. In some cases, differentiation between toxicity and rejection may be very difficult; complicated algorithms for dealing with this problem are not necessary. A careful dose reduction may answer the question in most of the cases. However, biopsies are also essential for three reasons [103]:

1. Nephrotoxicity can occur with CsA levels within or even below the therapeutic range.
2. Reduction of CsA dose, though improving renal function, does not always restore it to normal; the patient may require additional anti-rejection therapy, since nephrotoxicity and rejection occur together.
3. The vascular endothelial damage caused by rejection can be enhanced by the effects of CsA on prostacyclin synthesis and vasomotor tone.

Nephrotic syndrome

The efficacy of CsA in the treatment of steroid-responsive minimal change nephrotic syndrome (MCNS) has been demonstrated in numerous reports [104–110], whereas it is less effective in focal segmental glomerulosclerosis (FSGS) [111–113]. Recently, more promising results were obtained in FSGS with the use of CsA plus high-dose prednisolone [114], but this needs further confirmation in controlled trials.

At present CsA is not recommended as the first drug for treating MCNS but only as a substitute for prednisolone in cases of steroid-dependent or steroid-toxic MCNS. In these, CsA is effective in preventing relapses even after complete withdrawal of steroids [112]. Most of the patients experienced further relapses if CsA was stopped, and became "CsA dependent". At a workshop on the efficacy of Sandimmun in glomerulopathies in Madrid in 1988, it was concluded that CsA has its place in patients who frequently relapse or are steroid dependent despite a previous course with cytotoxic drugs. Cytotoxic drugs like cyclophosphamide or chlorambucil are superior at inducing long-term remission, however, if they fail the only means

of overcoming the severe side-effects of steroid treatment is to use CsA.

In our experience, CsA should be started when remission is induced by steroids since CsA has an anti-diuretic effect which reduces water retention in the severe nephrotic state. Once remission is induced and CsA levels are in the therapeutic range, steroid treatment can be discontinued. In about 90% of patients, remission can be sustained with CsA alone as long as the drug is given [115]. The starting dosage of CsA should be 150 mg/m^2 per day (in two divided doses) which corresponds to 4–6 mg/kg as used in adults but which better meets the dose requirements of smaller children. Dosages should be adjusted to reach blood trough levels in the range of 80–160 ng/ml if measured with the monoclonal RIA. This is analogous to 200–400 ng/ml if measured with the polyclonal RIA. This dosage and blood trough range has been shown to be unlikely to produce chronic CsA-induced nephropathy in a large series of patients with auto-immune diseases [113]. However, this could not be entirely excluded [116]. Therefore, we try to stop CsA after 6 months in order to test if there is further need for treatment. During long-term use it is advisable to taper the CsA dose down to the patient's individual threshold, and if he/she experiences a relapse to increase it to the previous step. Biopsies should be taken every 1–2 years during CsA treatment to obtain information about the effects of long-term CsA usage.

Trough levels should be measured twice weekly during the first 2 weeks in order to adjust the dosage; thereafter measurements every 2 weeks are usually sufficient. When patients need more than 200 mg/m^2 to achieve adequate blood levels, pharmacokinetic profiles and measurements of metabolites should be carried out as recommended above for patients with renal transplants. The same holds true for the use of drugs which interfere with cytochrome P-450 or which cause additive nephrotoxicity.

CsA must be used with more caution in patients with FSGS since kidneys with pre-existing damage are more susceptible to developing CsA nephrotoxicity; CsA should not be used if the glomerular filtration rate (GFR) is below 40 ml/min per 1.73 m^2. In patients with rapid deterioration of renal function it may be impossible to differentiate between the natural course of FSGS and toxicity; CsA must be immediately stopped in these cases.

Systemic lupus erythematosus and other nephropathies

A controversy exists about the efficacy of CsA in SLE. While some authors report improvement of severe SLE with the use of CsA [117–120], others have seen deterioration under CsA treatment [121, 122]. There are no controlled trials which document any benefit of CsA. Therefore, its use should be restricted to severe cases only. We use CsA in patients whose clinical course cannot be controlled by acceptable doses of steroids and azathioprine or cyclophosphamide. If the required high doses of steroids lead to severe steroid toxicity, a trial with CsA seems to be justified in order to lower the steroid doses. As in FSGS the GFR must be higher than 40 ml/min per 1.73 m^2. We start with a dose of 100 mg/m^2 and increase the dose to 150 mg/m^2 if it is tolerated by the patient. Target trough levels are the same as in nephrotic syndrome. We have the impression that our patients have benefited from CsA treatment [120]. Proteinuria decreased and the maintenance dose of steroids necessary to control the disease could be reduced. Feutren et al. [117] reported clinical improvement of severe SLE with CsA, interestingly, without improvement in serological parameters.

In other nephropathies such as IgA nephropathy, Henoch-Schoenlein nephritis, membranoproliferative glomerulonephritis and membranous glomerulonephritis, the benefit of CsA therapy is questionable. As reviewed by Graffenried et al. [113], complete remission was obtained in only 16% of patients, although CsA reduced proteinuria in 34%, which was called partial remission. We are reluctant to use CsA in these cases until a clear benefit is confirmed by controlled trials.

Conclusions

In the last 8 years knowledge of CsA has increased tremendously. Pharmacological behaviour has been studied extensively and mechanisms of toxicity are better understood. Nowadays, CsA can be regarded as a safe drug if all the knowledge of bioavailability, metabolism and drug interactions is considered. In children the different pharmacokinetics should be taken into account. Monitoring is essential for safe and effective use. Precise knowledge of the nature of the laboratory method employed for CsA determination and the spectrum of measured metabolites is essential for the physician treating patients with this drug. Different diseases may require different dosing regimes.

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Literature abstract

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Paramedian versus midline incision for the insertion of permanent peritoneal dialysis catheters

Ellen Ejlersen, Kenneth Steven, and Hans Løkkegaard

A randomized trial was conducted to examine the influence of the site of catheter insertion on the mechanical complications associated with the use of peritoneal dialysis catheters (pericatheter leakage/herniation and tip migration). 37 patients requiring a dialysis catheter for future CAPD were randomized to insertion by either a midline (prior standard approach) or a lateral incision (new approach). Thirteen catheters (6 midline, 7 lateral) failed for mechanical reasons – mainly irreversible tip migration. The one year estimated catheter survival without mechanical failure was found to be similar in the two groups: midline (59%) and lateral (51%), ($0.4<p<0.5$).