

## Other agents

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### GUIDELINES

**There is limited evidence to suggest that the progression of certain forms of renal disease are retarded by ibopamine. (Level II evidence; single RCT with suboptimal design; clinically relevant outcome; moderately strong effect) However, this benefit is outweighed by the serious side-effects of ibopamine (3-fold increased risk of death) and its use cannot be recommended.**

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions based on level III and IV sources)

- **There is limited evidence to suggest that the progression of certain forms of renal disease is retarded by non-steroidal anti-inflammatory drugs (NSAIDs) (Level III evidence; several retrospective and prospective cohort studies; mostly surrogate outcome measures; consistent weak effect) and by combined ketaconazole and prednisone (Level II–III evidence; single small cross-over study; clinically relevant outcome; weak effect). However, these benefits are outweighed by the serious side-effects of these medications and their use cannot be currently recommended.**

### Background

Animal studies have suggested renoprotective benefits associated with the administration of ibopamine (an orally active dopamine agonist with renin-angiotensin system blocking activity) and NSAIDs. Moreover, based on earlier case series demonstrating a correlation of renal failure progression with urinary excretion of 17-hydroxycorticosteroid (Walser and Ward 1988) and free cortisol, some investigators have hypothesised that combined therapy with ketaconazole (an inhibitor of cortisol production) and 2.5 mg prednisone (to prevent increased ACTH release but still allowing reduced total steroid activity) may retard renal failure progression. The objectives of this guideline are to evaluate the clinical evidence that ibopamine, NSAIDs and combined ketaconazole and prednisone therapy retard renal failure progression in humans.

### Search strategy

**Databases searched:** Medline (1999 to November Week 2, 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for non-steroidal anti-inflammatory drugs, dopamine agonists and cyclo-oxygenase 2 inhibitors. The results

were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialised Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.

**Date of search:** 16 December 2003.

## **What is the evidence?**

### **Ibopamine**

There have been one randomised controlled trial (RCT) (Stefoni et al 1996) and three prospective, non-controlled trials (Docci et al 1986, Russo et al 1990, Stefoni et al 1982) (all but 1 trial were reported by the same group).

Ibopamine is an orally active dopamine agonist which has been shown to activate dopaminergic receptors DA1 and DA2 at daily doses of 100–200 mg,  $\beta$ -adrenergic receptors at 300–400 mg, and  $\alpha$ -adrenergic receptors at greater than 400 mg (Itoh 1991, Dei Cas et al 1989). Its pharmacological effect is maintained over prolonged periods (Itoh et al 1992, Dei Cas et al 1988). Both in normal subjects and in patients with mild renal impairment, ibopamine administration has produced an increase in renal plasma flow, an increase in  $^{99m}\text{Tc}$ -DTPA clearance, a reduction in filtration fraction and an increase in sodium excretion and diuresis (Kasmer et al 1990, Stefoni et al 1981, Melloni et al 1981).

Stefoni et al (1996) conducted a prospective, randomised, open-label, multicentre trial of ibopamine in patients with mild-to-moderate chronic renal disease (CKD) (plasma creatinine 1.5–4.0 mg/dl). A total of 189 patients from 11 nephrology centres were randomly allocated to receive ibopamine 100 mg omni die ( $n = 96$ ) or no treatment ( $n = 93$ ). Allocation concealment was inadequate. Exclusion criteria included diabetes mellitus, resistant hypertension with diastolic blood pressures of 100 mmHg or more, NYHA class III–IV congestive cardiac failure, nephrotic range proteinuria, pregnancy, rapid renal function deterioration ( $> 30\%$  in plasma creatinine over preceding 6 months) and patients receiving steroids, cytotoxics or ACE inhibitors. Ibopamine compliance was not formally assessed. Both groups were comparable at baseline. 93 % of patients completed the first year of observation and 78% reached the end of the whole 2-year study. Drop-out rates were nearly identical in both groups. Four (4.2%) patients withdrew from the ibopamine group due to drug intolerance (epigastric pain or tachycardia). Adverse effects were more common in the ibopamine group (40 vs 20 or 42% vs 22%), but the statistical significance and breakdown of these events were not reported. Renal function survival curves were significantly improved in the ibopamine-treated group. Mean plasma creatinine rose by 17% in the ibopamine group and by 36% in controls. Creatinine clearance decline was significantly reduced by ibopamine (5% vs 14%). Ibopamine exerted a significant positive effect on renal function compared with controls in both patients with mild (creatinine 1.5–2.5 mg/dL) and moderate (creatinine 2.6–4.0 mg/dL) renal impairment. Ibopamine-treated patients experienced an initial increase in creatinine clearance (not seen in the controls), raising the possibility that ibopamine exerted an early haemodynamic and/or tubular secretory effect. The main limitations of the study were: (a) the use of plasma creatinine and

creatinine clearance to evaluate renal function (the effect of ibopamine on tubular secretion of creatinine has not been studied); (b) inadequate allocation concealment which could have potentially introduced physician bias; (c) high drop-out rates (22%); and, (d) the exclusion of ACE inhibitors (thus it is not known whether the effects of ibopamine would be additive with these agents). The latter point may be particularly relevant since ibopamine has been shown to exert an antagonistic effect against angiotensin II at both a glomerular and tubular level (Itoh et al 1992, Felder et al 1989). It also directly reduces activation of the renin-angiotensin system and inhibits aldosterone secretion (Lopez Sendon 1990, Girbes et al 1991, Missale et al 1989).

Three prospective, non-controlled, small studies by single centres (Docci et al 1986, Russo et al 1990, Stefoni et al 1982) have reported a significant improvement in renal function indices (plasma creatinine, reciprocal plasma creatinine or creatinine clearance) in patients with mild-to-moderate CKD treated with ibopamine 100 mg daily for periods ranging from 6 to 24 months.

Significant concerns regarding the safety of ibopamine have been raised by the PRIME II study, which showed that ibopamine was associated with an increased risk of death in patients with NYHA class III and IV heart failure (Hampton et al 1997), particularly in patients with renal impairment. A subsequent nested case-control study in users of ibopamine in the Netherlands (Stricker et al 1997) demonstrated that patients with a serum creatinine level in the highest quartile had a 3-fold increased risk of death on ibopamine.

### **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

There are no RCTs or prospective studies. NSAIDs have generally been avoided in the setting of chronic kidney disease (CKD) because of frequent reports of deterioration of renal function following administration of these compounds. However, two retrospective studies have suggested a benefit of NSAIDs on the progression of renal insufficiency (Vriesendorp et al 1986 B, Lagrue et al 1988).

Numerous prospective uncontrolled studies (Fieschi et al 1955, de Vries et al 1960, Michielsen and Lambert 1967 A, Michielsen and Lambert 1967 B, Conte et al 1967, Vercellone et al 1969, Wijdeveld 1971, Donker et al 1978, Vriesendorp et al 1986 A) and a double-blind, crossover study (Vriesendorp et al 1985) have reported a significant antiproteinuric effect of NSAIDs (primarily indomethacin) in nephrotic patients. The proportional decrease in proteinuria exceeded the associated 12–36% fall in GFR (eg for indomethacin, the fall in proteinuria/GFR was 53%) (Vriesendorp et al 1986 B). Suppression of proteinuria can be sustained for up to 3 years of treatment (Vriesendorp et al 1986 B), but tends to reverse to pretreatment levels on discontinuation of the drug.

Vriesendorp et al (1986) B, retrospectively studied the influence of indomethacin on renal function decline and renal outcome in 114 patients with nephrotic syndrome due to membranous nephropathy, focal segmental glomerulosclerosis or membranoproliferative glomerulonephritis. Fifty-eight patients received indomethacin (median dose 150 mg, range 75–225 mg) for a median period of 3 years (range 0.5–9 years) during the period between 1968 and 1983. Forty untreated patients were used as controls, although 5 of these had received indomethacin for up to 1 month. Sixteen

patients were excluded because follow-up was less than 6 months. None of the patients had received corticosteroids or cytotoxic agents. Compared with controls, indomethacin-treated patients had significantly lower plasma creatinine concentrations, lower mean arterial pressures and higher 24-hour urinary protein excretion rates at baseline. Renal survival was significantly better in the indomethacin-treated patients with only 31% reaching dialysis at 10 years (c.f. 66% of controls). However, when the endpoint of creatinine doubling time was used in the analysis, no significant difference was observed between the 2 groups. A subsequent analysis suggested that only patients with a creatinine < 0.11 mmol/L benefited significantly from indomethacin treatment. Significant side-effects of treatment, (such as azotaemia or gastrointestinal haemorrhage), were not mentioned in the paper. The major limitations of the study include: (a) the likelihood of serious recall bias and case selection bias as a result of the retrospective design; (b) the lack of comparability of the indomethacin-treated and control groups (the former had less severe renal functional impairment and lower blood pressure); (c) the high exclusion rate (14%) due to incomplete follow-up; (d) failure to make appropriate statistical adjustments for the differences in renal function, blood pressure and proteinuria between the 2 groups; and, (e) use of a log-rank analysis for renal survival rather than a Cox's proportional hazards model (which could be used to adjust for potentially confounding factors).

Laguer and associates (Laguer et al 1988) also reported a retrospective analysis of the effect of indomethacin on renal failure progression in 53 nephrotic patients with membranoproliferative glomerulonephritis. They similarly reported an improvement in renal survival but based this on comparisons with published literature regarding the natural history of untreated disease (obviously inappropriate).

### **Inhibitors of Endogenous Cortisol Synthesis**

There are no RCTs.

Based on earlier case series demonstrating a correlation between renal failure progression and urinary excretion of 17-hydroxycorticosteroid (Walser and Ward 1988) and free cortisol, (Walser 1990, Walser and Hill 1997) Walser et al performed a small, prospective, crossover study of combined administration of 200–600 mg daily of ketoconazole (an inhibitor of cortisol production) and 2.5 mg prednisone (to prevent increased ACTH release but still allowing reduced total steroid activity) in 24 patients with progressive renal failure. Four patients were withdrawn because of severe ketoconazole side-effects and one patient was withdrawn because of the development of oliguric acute-on-chronic renal failure. A variety of crossover designs were employed in the remaining 19 patients, including AB (n = 10), BA (n = 3), ABA (n = 3) and ABAB (n = 3). "Randomisation" of patients to a particular crossover design was by an "individual not involved in the study." To estimate the effect of treatment on GFR, estimated by <sup>99m</sup>Tc-DTPA clearance, a linear spline technique was used. The durations of each study period were quite variable between patients but were of the order of 3–11 months. Significant slowing of GFR decline was observed for patients with chronic glomerular disease, interstitial nephritis and diabetic nephropathy, but the treatment was associated with an acceleration of GFR decline in patients with polycystic kidney disease (n = 5). The study was obviously too small with too short a follow-up time to draw any conclusions regarding the value of this therapy. Moreover, the design and

statistical analysis were suboptimal and the serious side-effects of the treatment were disconcerting.

## **Summary of the evidence**

Ibopamine has been shown in one moderately large RCT with inadequate allocation concealment to be associated with a statistically significant and clinically meaningful reduction in GFR decline in mild-to-moderate chronic renal failure. However, Ibopamine administration has also been shown to be associated with significant harm (including an increased risk of death), which outweighs its renoprotective benefits.

There are no RCTs of NSAID therapy in the chronic renal failure. However, limited retrospective and prospective cohort studies involving nephrotic patients suggest a benefit of NSAID, as evidenced by an antiproteinuric response and, in some cases, by a retardation of renal function decline. Significant adverse effects were noted in several studies.

One small, prospective, crossover study of combined administration of ketaconazole and prednisone in 24 patients with chronic renal failure observed a significant slowing of GFR decline (except in polycystic kidney disease where GFR decline was accelerated). These benefits appeared to be outweighed by serious side-effects.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**British Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

## **Implementation and audit**

No recommendation.

## **Suggestions for future research**

No recommendation.

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## Appendices

**Table 1 – Characteristics of included studies**

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Stefoni S, 1996	189	Randomised controlled clinical trial	11 nephrology centres in Italy	Patients aged 18–70 yrs with mild or moderate chronic renal failure	Ibopamine supplement of 100 mg/day in addition to routine medical treatment N = 96	No Ibopamine therapy N = 93	24	

**Table 2 – Quality of randomised trials**

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Stefoni S, 1996	Statistical software package	No	No	No	Unclear	7% (after 12 months) 22% (after 24 months)

\* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.