

Analgesic-Associated Kidney Disease

Date written: July 2005

Final submission: September 2005

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GUIDELINES

- a. Analgesic intake should be discontinued in patients with analgesic nephropathy. (Level II– III evidence)**
- b. Non-selective COX-1 and COX-2 inhibitors (with the specific exception of low dose aspirin) should be avoided, where possible, in patients with hypertension, as their use is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy. (Level I evidence)**
- c. Analgesic and anti-inflammatory therapy form an important component of the management of a variety of chronic degenerative diseases. (Level I evidence) The beneficial effects of these agents should be balanced against the risk of progressive renal damage and hypertension associated with their chronic and habitual use.**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **Continued analgesic intake is associated with an increased faster rate of decline of renal function and increased risk of end-stage kidney disease (ESKD) in patients with analgesic nephropathy. (Level II-III evidence; large prospective cohort studies; clinically relevant outcomes; consistent strong effects).**
- **Cessation of analgesic use has been associated with retardation of kidney failure progression. (Level II-III evidence; several retrospective cohort studies; clinically relevant outcomes; variable effects).**
- **The use of non-selective COX-1 and COX-2 inhibitors is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy. (Level I-II evidence; large meta-analyses and RCTs, clinically relevant outcomes; consistent strong effects)**

Background

Combinations of antipyretic analgesics taken in large doses over long periods of time are associated with the development of a slowly progressive kidney disease characterised by papillary necrosis and interstitial scarring. Currently, at least 6% of patients reaching ESKD in Australia have analgesic nephropathy (ANZDATA). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of interventions on renal functional decline in analgesic nephropathy (AN).

This guideline does not address the known associations between AN and malignancy, peptic ulcer disease and cardiovascular disease that may be positively influenced by habitual analgesic use.

Search strategy

Databases searched: The search for MeSH terms and text words for analgesic nephropathy was carried out in Medline (1966 to September Week 2 2004).

Date of search: 17 September 2004.

What is the evidence?

Habitual analgesic use has been associated with renal impairment and progression to ESKD in a number of large prospective cohort studies:

- 200 patients with active analgesic abuse were followed for 7 years and the rate of decline in renal function compared to age-matched controls. Renal function decline was significantly greater in patients with ongoing analgesic abuse, including a 6.1 times relative risk of renal impairment compared to the control population (Elseviers et al, 1995).
- In a large prospective, longitudinal, epidemiological study of 623 healthy women 30–49 years old who had evidence of a regular intake of phenacetin and a matched control group of 621 women, the relative risk for deaths due to urological or kidney disease was 16.1 (95%CI: 3.9–66.1) (Dubach UC, 1986–87).

There are no randomised controlled trials (RCTs) in AN.

Australia and New Zealand Dialysis Registry data shows a progressive decline in AN as a cause of ESKD after the withdrawal of phenacetin from compound analgesics in Australia (McCredie 1989).

In prospective, observational, cohort studies, continued use of analgesics has been associated with an accelerated rate of progression of renal insufficiency in AN (MacKinnon et al 1989, Hauser et al 1991)

In retrospective, cohort studies, patients with analgesic nephropathy who discontinued using analgesics were less likely to develop ESKD, than those who continued their consumption of analgesics (Gonwa et al 1981, Kindler et al 1990). Cessation of analgesic intake may also slow the rate of loss of renal function, even when renal insufficiency is well advanced (McCredie et al 1989).

Recent case-control studies have raised the possibility that habitual analgesic use could increase the likelihood or rate of progression of chronic kidney disease (CKD) per se. In the study by Sandler et al (1989), the odds ratios for the development of CKD was highest for patients with interstitial nephritis and renal insufficiency of unknown cause who habitually used analgesics. However, there was a borderline increase in the odds ratios for patients with a diagnosis of nephrosclerosis, diabetic nephropathy, and glomerulonephritis. Similarly, Perneger et al (1994) found the

increased risk of CKD was similar in the four groups of patients with renal disease due to diabetic nephropathy, hypertension, other specific causes, and unknown causes. However, there is currently insufficient evidence for a causal association between habitual use of analgesic and an increased risk of ESKD.

Regular use of analgesic drugs containing phenacetin is associated with an increased risk of hypertension (a known risk factor for progressive nephropathy).

- In a large prospective, longitudinal epidemiological study of 623 healthy women 30–49 years old who had evidence of a regular intake of phenacetin and a matched control group of 621 women, the odds ratio for the incidence of hypertension was 1.6 (95%CI: 1.2– 2.1) (Dubach et al 1991). Some of this reflects the increased risk of cardiovascular disease and kidney disease.

Similarly, regular use of non-selective COX-1 and COX-2 inhibitors is associated with an increased risk of hypertension and destabilisation of blood pressure control in patients with hypertension.

- Two separate meta-analyses that examine the effects of non-selective COX-1 inhibitors including over-the-counter preparations such as naproxen, indomethacin, and ibuprofen implicate them as contributing to loss of BP control and reduction in efficacy of antihypertensive drug therapy (Johnson et al 1994, Pope et al 1993).
- COX-2 inhibitors have also been associated with destabilization of blood pressure control in RCTs (Sowers et al 2005).

It should be noted that chronic low-dose aspirin has not been associated with detrimental effects on blood pressure control (Avanzini et al 2000, Johnson 1994; Nawarskas et al 1999).

Summary of the evidence

Therapy with non-selective COX-1 and COX-2 inhibitors is associated with loss of BP control and reduction in efficacy of antihypertensive drug therapy in some patients. As blood pressure control is a key component part of the management of patients with CKD, it is recommended that these agents should be avoided, where possible, in patients with CKD. This recommendation does not apply to low dose aspirin, which has neutral effects on BP control, together with beneficial effects on cardiovascular outcomes.

Analgesic intake should be discontinued in patients with analgesic nephropathy, as early as possible, to have the greatest likelihood of slowing the progressive kidney scarring associated with habitual analgesic use.

Analgesic and anti-inflammatory therapy form an important component part of the management of a variety of chronic degenerative diseases. The beneficial effects of these agents should be balanced against the risk of progressive kidney damage and hypertension associated with their chronic and habitual use.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Attempts should be made to prevent and correct acute decline in GFR. Frequent causes of acute decline in GFR include non-steroidal anti-inflammatory agents, including cyclo-oxygenase type 2 inhibitors;

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Analgesic-Associated Kidney Disease. NIH Consensus Statement 1984: (Kindler et al 1990).

The main strategies of management must include:

1. Avoidance of antipyretic-analgesic agents, as well as non-steroidal anti-inflammatory drugs.
2. Prompt treatment of proven urinary tract infections.
3. Awareness that a necrotic papilla may slough and obstruct the urinary tract, sometimes requiring prompt intervention to prevent further loss of renal function.
4. Careful supervision of hypertension.
5. Recognition that tumours of the urinary tract may occur more frequently in patients with analgesic nephropathy. Unexplained episodes of haematuria, including a marked increase in microscopic haematuria, should therefore be evaluated carefully.
6. Consideration of the non-renal manifestations of the analgesic abuse syndrome.

Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy: (Feinstein AR, et al. 2000)

1. There is insufficient evidence to associate non-phenacetin combined analgesics with nephropathy.
2. New studies should be done to provide appropriate data to resolve the question.

US Food and Drug Administration (FDA): Analgesic combination containing paracetamol, aspirin, and caffeine is safe and effective for the use in uncomplicated migraine.

Implementation and audit:

No recommendation.

Suggestions for future research:

The recent reintroduction of compound analgesics containing paracetamol and caffeine as OTC medications in New Zealand and Asia (but not Australia) should be closely monitored by renal physicians.

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