LEADING ARTICLE

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Analgesic Nephropathy

Is it Caused by Multi-Analgesic Abuse or Single Substance Use?

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Abstract

Analgesic nephropathy is a slowly progressive renal disease, characterised by renal papillary necrosis. Recently, diagnostic criteria for this disease have been defined based on renal computed tomography scanning performed without contrast. The observation of a decreased renal mass of both kidneys, combined with either bumpy contours or papillary calcifications, has been found to have high diagnostic specificity and sensitivity. However, the question remains as to what kind of analgesics can cause analgesic nephropathy.

In the majority of early reports about this condition, phenacetin was singled out as the nephrotoxic culprit. However, during the last decade the nephrotoxic potential of nonphenacetin-containing preparations has become apparent. It is clear that people who abuse analgesics prefer combination analgesics containing 2 analgesics combined with caffeine and/or codeine. In contrast, abuse of products containing only aspirin (acetylsalicylic acid) or paracetamol (acetaminophen) is seldom described and associated renal disease is only occasionally reported.

Experimental evidence of the nephrotoxicity of analgesic preparations is not well established. The results of studies involving analgesic administration in animals remain contradictory.

Clinical evidence linking high consumption of analgesic preparations with analgesic nephropathy is overwhelming. Most patients who admit to overconsuming analgesics have taken preparation containing more than one compound. In recent years, it has become more apparent that preparations not containing phenacetin also have the potential to cause nephrotoxicity manifesting as identical renal lesions. Further epidemiological evidence of the nephrotoxic potential of analgesic combinations has come from case-control studies published during the last decade and from 2 prospective cohort studies.

Effective prevention of analgesic nephropathy consists of the prohibition of over-the-counter sales of preparation containing at least 2 analgesics associated with caffeine and/or codeine.

The nephrotoxic potential of different kinds of analgesics remains a controversial issue. In nearly all the initial reports of analgesic nephropathy,[1-4] patients had taken large amounts of products containing phenacetin. This led to the hypothesis that phenacetin was solely responsible for the development of the nephrotoxicity and so it was termed 'phenacetin nephritis'. However, in the late 1970s, it became apparent that the abuse of different kinds of analgesic preparations induced severe renal

damage, whether they contained phenacetin or not. The disease was then more appropriately renamed analgesic nephropathy.

Analgesic nephropathy has been and still is a serious problem in several countries. Structured information concerning the extent of the problem is limited to the US, Europe and Australia. In the early 1990s, the incidence of analgesic nephropathy among patients receiving dialysis was estimated to be 0.8, 3 and 9%, respectively, in the US, Europe and Australia.[5-7] In the 1970s, the incidence of analgesic nephropathy in Australia was 22% and this was considered to be the highest in the world; however, a decrease was observed after restriction of the sales of over-the-counter analgesics in 1979.[8,9] Also, in several Western European countries a decrease in the national incidence of analgesic nephropathy has been observed in recent years. In contrast, analgesic nephropathy has gained recognition in Eastern Europe, and unexpectedly high incidences have recently been measured in Czech and Slovak Republics[10] and Hungary.[11]

In Australia, Western Europe and the US, phenacetin-containing preparations were discontinued 10 to 20 years ago. However, over the last decade scientists have demonstrated that there is a risk of renal disorders with analgesic preparations that do not contain phenacetin and many clinicians have diagnosed analgesic nephropathy in patients who have never consumed phenacetin. The publication of a study investigating the nephrotoxic potential of paracetamol (acetaminophen),[12] the investigation into the possible contribution of analgesics to the progression of chronic renal failure,[12,13] and the recommendations of the National Kidney Foundation of the US[14] have revived the discussion concerning the nephrotoxicity of the many analgesic combinations that are currently available.

Nephrotoxicity as considered in this review deals with, and is limited to, 'classic' analgesic nephropathy. This particular form of renal disease is characterised by renal papillary necrosis and chronic interstitial nephritis associated with abuse of analgesic mixtures. Nonsteroidal anti-inflammatory drug-related renal toxicity, mainly presenting as acute renal failure and serious fluid and electrolyte disorders, is excluded from this discussion.

1. Diagnosis of Analgesic Nephropathy

Analgesic nephropathy is a slowly progressive renal disease which generally remains asymptomatic until 70 to 85% of the renal function is lost.[15]

Most patients who were ultimately diagnosed as having analgesic nephropathy only attended an nephrological outpatient clinic when renal failure had reached a chronic and advanced stage.[16,17] End-stage renal failure due to analgesic abuse was observed after patients had been abusing these agents for 5 to 55 years and most patients with analgesic nephropathy began chronic renal replacement therapy when they were 50 to 60 years old.[8,9,16,17]

Reported symptoms of analgesic nephropathy fit within the general clinical picture of progressive renal insufficiency and are mainly nonspecific. Patients with analgesic nephropathy have tubulomedular dysfunction characterised by a decrease in concentration and acidification ability. It is seldom clearly observed that a patient has eliminated a necrotised papilla. If this does occur, the patient will present with renal colic and macroscopic haematuria. In most patients with analgesic nephropathy, proteinuria is limited and urine volume remains high. Sterile pyuria and recurrent urinary tract infections are described in up to 60 and 75% of patients with analgesic nephropathy, respectively. Renal papillary necrosis associated with calcifications is considered as the hallmark of analgesic nephropathy.

Since analgesic nephropathy is associated with mainly nonspecific clinical manifestations, the diagnosis of analgesic nephropathy can be problematic. Until the 1990s, the most important argument in favour of a diagnosis of analgesic nephropathy was the frequently biased demonstration of a history of analgesic abuse in the absence of any other aetiology for the renal insufficiency. Recently, criteria have been defined for the diagnosis of this disease based on a computerised tomography scan

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investigation carried out without the use of contrast material.

The diagnostic criteria were selected in Belgium[16] and evaluated in 22 European centres during the Analgesic Nephropathy Network Europe (ANNE) Study.[17] The observation of a decreased renal mass of both kidneys combined with either bumpy contours (3 or more indentations), or papillary calcifications, was found to have a high diagnostic specificity and sensitivity.[18] Even in patients with incipient-to-moderate renal failure (serum creatinine level <4 mg/dl), these renal imaging criteria showed a sensitivity of 92% with a specificity of 100%.[19]

2. Which Kinds of Analgesics are Nephrotoxic?

In the majority of the early reports of analgesic nephropathy, phenacetin was singled out as the nephrotoxic culprit on the basis of association and circumstantial evidence. Nearly all patients initially described, had taken large amounts of analgesic mixtures containing phenacetin. Prescott[20] was the first to evaluate the nephrotoxic role of phenacetin compared with other analgesics. He stated that in the past insufficient attention had been given to the possible nephrotoxicity of the other analgesics invariably taken with phenacetin, and that the common belief that phenacetin was the primary cause of analgesic nephropathy could be challenged on many counts.

The withdrawal of phenacetin from analgesic preparations in Western Europe and the US, provided a reason to investigate the nephrotoxic potency of different kinds of analgesic products. Although in the 1980s, case series of analgesic nephropathy were reported from all over the world, evidence for the nephrotoxic effect of these other analgesics remained mainly limited to local observations that did or did not control for previous intake of phenacetin-containing products.

The long-standing excessive use of analgesics observed in patients with analgesic nephropathy is concentrated on combination analgesics. People who abuse analgesics prefer combination analgesic products to products containing single analgesics and they take these combination products for their mood-altering effects rather than for the relief of physical complaints. Hence, most of the abused preparations contain caffeine and/or codeine, and it is clearly established that the addition of these substances plays an important role in the creation of dependency.[21]

In contrast, abuse of products containing only aspirin (acetylsalicylic acid) or paracetamol is seldom described.[22] Consequently, although experimental nephrotoxicity of single analgesics exists, renal disease associated with single analgesic consumption in humans is only occasionally reported. The nephrotoxic effect of phenacetin used as a single analgesic could not be investigated in humans, since phenacetin was only available in analgesic mixtures.

The nephrotoxic potency of aspirin used as a single analgesic has been investigated in patients with rheumatoid arthritis where high-dose salicylate therapy has been the mainstay of treatment. In the studies of Ferguson et al.[23] and Emkey and Mills,[24] it was concluded that long term salicylate ingestion does not cause renal damage. Other studies failed to give conclusive results because of their inability to control for the other analgesics taken in addition to the high doses of aspirin consumed.[20] Control for additional consumption of other analgesics was also lacking in the case control study by Morlans et al.,[25] where an increased risk of nephropathy was seen with aspirin, when it was used as a single analgesic.

The nephrotoxic effect of paracetamol used as a single analgesic was suggested by the clinical observation by Segasothy et al.[26] who found 15 patients with renal papillary necrosis that was attributable to paracetamol consumption. However, a reliable control for other analgesics taken by these patients is lacking. The case control studies of Sandler et al.[13] and Perneger et al.[12] were in support of these clinical observations, showing increased risk ratios for nephrotoxicity associated with the consumption of paracetamol. However, in both studies paracetamol was taken as part of an

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unspecified mix of single agents and combinations.[27]

The available information, based on a critical analysis of the available literature, suggests habitual consumption of both phenacetin-containing preparations and non–phenacetin-containing preparations is associated with analgesic nephropathy.[18,28] Recently, the *ad hoc* committee of the National Kidney Foundation in the US[14] as well as a group of European scientists who were experienced in this field[29] stated clearly that analgesic nephropathy is caused by the excessive use of different kinds of analgesic preparations containing 2 analgesic components combined with caffeine and/or codeine.

3. Experimental Evidence

Experimentally, the nephrotoxicity of analgesics has been studied since 1955, mainly using rats fed with large amounts of drugs, sometimes aggravating the renal effects by dehydration or by introducing bacteria into the blood, peritoneum or bladder. The results of analgesic administration in animals are somewhat contradictory.[30]

In table I, the results of single analgesic administration and several kinds of mixtures tested in highly sensitised Gunn rats were compared. It could be concluded that renal papillary necrosis was most frequently observed after the administration of aspirin alone or in combination with phenacetin or paracetamol.[31] In his recent review of the experimental data, Porter[30] concluded that aspirin seems to be the most nephrotoxic of the commonly available analgesics. He stated that when aspirin is combined with other analgesics, the limited data available suggest at least an additive nephrotoxic effect, if not a synergistic effect.

A possible explanation for the synergistic toxicity of analgesics has been proposed by Duggin (fig. 1).[32] He suggested that the following steps might occur if a combination of phenacetin and/or paracetamol and aspirin is ingested. Phenacetin is converted in the gut and liver to paracetamol by first-pass metabolism. Paracetamol is then taken up by the kidney and excreted. During its excretion, paracetamol becomes concentrated in the papillae of the kidney during physiological degrees of antidiuresis, the concentration being up to 5 times the intracellular concentration of other tissues.

Table I. Experimental evidence of the nephrotoxicity of different kinds of analgesics: renal papillary necrosis in Gunn rats (reproduced from Nanra & Kincaid-Smith,[31] with permission)

Drug	Dosage (mg/kg/day)	Duration of dosing (wks)	Renal papillary necrosis		Chronic interstitial nephritis (%)
			%	grade	
Phenacetin	320-500	4	7	+	
	1150	Single dose	33	+	
Paracetamol (acetaminophen)	268-420	4	37	+	
Paracetamol + uninephrectomy	538	Single dose	85	+	+
Aspirin (acetylsalicylic acid)	200-500	3-4	45-63	++	
	175-1150	Single dose	17-100	++	
Aspirin + uninephrectomy	225	Single dose	90	++	
Sodium salicylate	480	Single dose	50	++	
Antipyrine + uninephrectomy	471	Single dose	80	++	40
APC	1190	5-18 days	100	++	
	238	25-34	70	++	
Aspirin + paracetamol	1182	Single dose	100	++	70
Antipyrine + paracetamol	1260	Single dose	95	++	75

APC = aspirin, phenacetin and caffeine.

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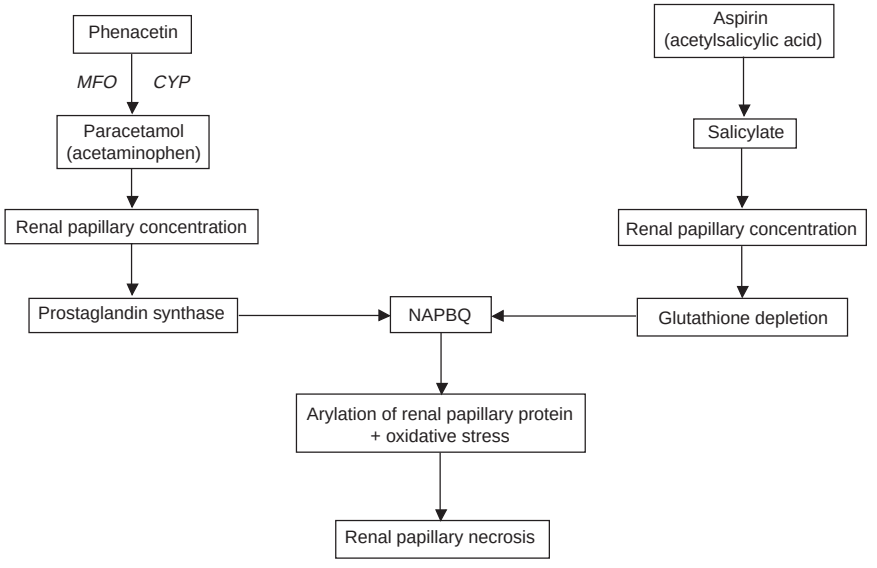

Fig. 1. Synergistic toxicity of analgesics in the renal inner medulla (reproduced from Duggin,[32] with permission.) **CYP** = cytochrome P450 enzyme system; **MFO** = mixed function oxidase system; **NAPBQ** = *N*-acetyl-*p*-benzoquineimine.

The prostaglandin hydroperoxidase component of the prostaglandin H synthase enzyme complex converts paracetamol to its reactive metabolite (probably by a one electron oxidation reaction and hydrogen abstraction) to form the phenoxyradical of paracetamol which then undergoes further oxidation to the more reactive intermediate *N*-acetyl-*p*-benzoquineimine. This metabolite reacts rapidly with reduced glutathione. If paracetamol is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the paracetamol is ingested with aspirin, the aspirin is converted to salicylate and salicylate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. With the cellular glutathione depleted, the reactive metabolite of paracetamol then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.

Additionally, experimental data are suggestive for the limited role of phenacetin in the development of analgesic nephropathy. In rats administered single and combined analgesics at high doses over a relatively short period, the incidence of renal papillary necrosis was the lowest in the single phenacetin group (reviewed by Prescott[20] and Schwarz[33]). Additionally, pharmacological studies in dogs and humans have shown that phenacetin undergoes first pass metabolism in the liver, generating paracetamol.[34,35] Consequently, even at high doses, ingested phenacetin barely reaches the kidney as such. It was concluded that the nephrotoxicity of phenacetin is not determined by phenacetin itself, but through its major metabolite paracetamol potentiated by the other analgesic agents present in the analgesic mixtures.

4. Clinical Evidence

In humans, there is overwhelming clinical evidence linking analgesic abuse with a particular form of chronic renal damage evolving towards end-stage renal failure. There are numerous reports demonstrating a high incidence of heavy analgesic consumption in patients with renal failure or papillary necrosis (reviewed by Prescott[20]). Also the observed deterioration of renal function in patients with analgesic nephropathy who continue their

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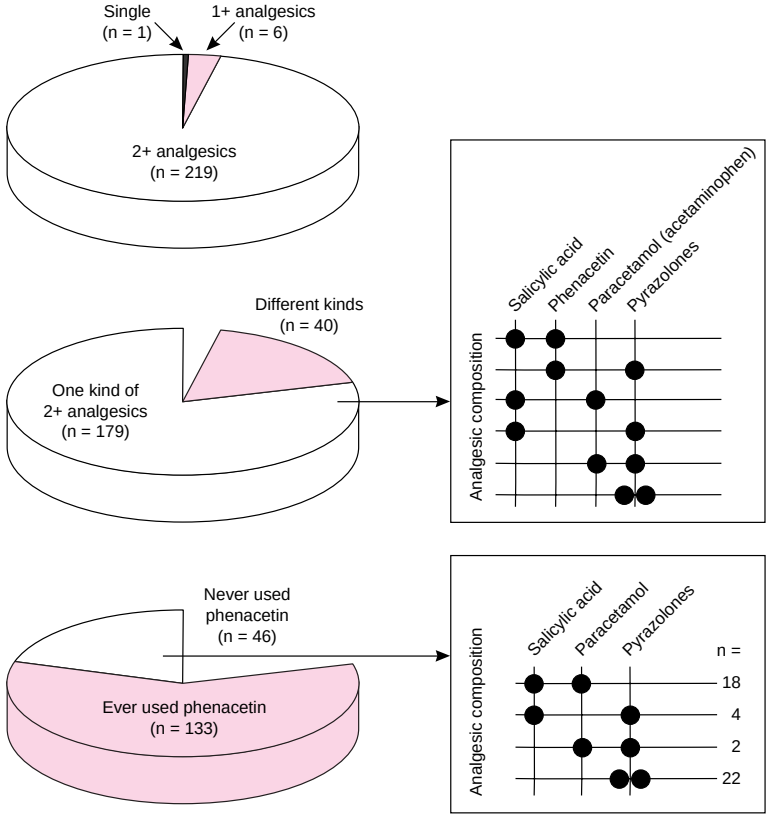

Fig. 2. Nephrotoxicity of analgesic preparations containing 2 analgesic components combined with potentially addictive substances (e.g. caffeine) [2+ analgesics]. **Top**: of 226 patients diagnosed as having analgesic nephropathy, 219 (97%) admitted the abuse of 2+ analgesics. 'Single' indicates that the product contains 1 antipyretic analgesic; '1+' indicates that the product contains an antipyretic analgesic plus caffeine and/or codeine. **Centre:** patients who had consumed different kinds of compound analgesic preparation were excluded, allowing the remaining 179 patients to be studied for particular analgesic combinations (see panel on right). **Bottom:** after the further exclusion of ever-users of 2+ analgesics containing phenacetin, 46 patients who had never used phenacetin were left. These patients were stratified according to the different analgesic combinations that they had use (see panel on right) [reproduced from Elseviers & De Broe,[40] with permission].

abuse, which contrasts with the stabilisation of renal function after discontinuation of the abuse, favours this association.[36-38]

Most patients who admit to overconsuming analgesics have taken preparations containing more than one compound. Moreover, during the 1980s, it became more apparent that preparations not containing phenacetin also had the potential to cause nephrotoxicity that manifested as identical renal lesions. The number of patients with a history of analgesic abuse who have never consumed phenacetin is increasing and more and more clinical observations mention nephrotoxicity linked to use of other kinds of analgesic preparations.[37,39]

Recently, the analgesic consumption of a cohort study of 226 patients with a clear diagnosis of analgesic nephropathy was investigated. Patients were recruited within the framework of diagnostic criteria studies in Belgium[16] (n = 130) and 11 other European countries (n = 96).[17,19]

In all patients, analgesic nephropathy was diagnosed using the same, recently developed, high performing renal imaging criteria as described in section 1.[19] For all patients, the history of abuse was

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documented by the same methodology using the same structured questionnaire accompanied by a picture book containing photographs of all analgesic products with a sales volume of more than 1% of the total volume sold in the country under consideration.

As shown in figure 2, all patients with analgesic nephropathy (except 7) admitted abusing analgesic preparations containing caffeine and/or codeine. In the absence of any previous phenacetin consumption, nephrotoxicity was documented in patients taking preparations containing a combination of: salicylic acid and paracetamol; salicylic acid and a pyrazolone; paracetamol and a pyrazolone; and 2 pyrazolones.[40] Pyrazolones included were phenazone (antipyrine), salicylphenazone (salipyrine), aminophenazone (aminopyrine) and dipyrone (mestamizol).

In addition, the minimum analgesic consumption required to develop analgesic nephropathy was calculated to be daily consumption for at least 5 years. None of the individuals with daily use of analgesic preparations for less than 5 years (n = 16), nor those with weekly consumption for more than 5 years (n = 19) met the renal imaging criteria of analgesic nephropathy.[17]

5. Epidemiological Evidence

The association between analgesic abuse and the development of renal impairment is documented in several case-control studies published in the 1980s. The studies were conducted in Australia,[41] the US,[12,13,42] Germany[43] and Spain.[25] Relevant methodological details are summarised in table II. In all studies except for the study by McCredie et al,[41] the matched controls were randomly selected. A history of analgesic consumption was obtained by direct interview of the participants except in the studies by Sandler et al.[13] and Perneger et al.[12] where telephone interviews were used. Moreover, in the Sandler et al.[13] study, the interviews were conducted using proxies for 55% of the patients and 10% of the control individuals.

The overall results shown in table II are odds ratios, estimating the relative risk for developing the disease under study when analgesics of any kind were taken in the minimum dose defined. The studies by Sandler et al.,[13] Pommer et al.[43] and Morlans et al.[25] resulted in comparable odds ratios showing a 2- to 3-fold increased risk for developing chronic renal failure after analgesic abuse. The study by McCredie et al.[41] used a more specific diagnosis of analgesic nephropathy (renal papillary necrosis) and the resulting odds ratio was considerably higher. The negative results obtained in the study by Murray and colleagues[42] can possibly be attributed to the low prevalence of analgesic nephropathy in the area investigated, and the minimum definition of analgesic abuse (i.e. almost daily for 1 month) employed.

The most firmly based evidence of an association is provided by the 2 prospective studies reported (table II). Dubach and coworkers[44] followed a cohort of working women aged 30 to 49 years with objective evidence of the intake of phenacetin-containing analgesics. Urine specimens of the women under study were analysed for the presence of *N*-acetyl-*p*-aminophenol (NAPAP), the main metabolite of phenacetin. Individuals with a positive result for NAPAP were considered as analgesic abusers. Based on the data from Dubach et al.,[44] the relative risk for developing renal failure after regular analgesic consumption of phenacetin-containing products in young women could be estimated to be 8.1 [95% confidence interval (CI): 2.8 to 23.2].[45]

A second prospective study extended the results of Dubach and colleagues,[44] to include individuals of different gender and age categories, who were abusing different kinds of analgesics containing or not containing phenacetin. A relative risk of 6.1 (95% CI: 1.4 to 25.9) was observed for the development of decreased renal function. Moreover, the renal impairment was found to be compatible with the diagnosis of analgesic nephropathy in most of the patients, in the absence of other causes of renal disease.[46]

Although both studies had substantial differences in terms of the study population, the analgesics included and the follow-up period, remarkable

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Table II. Epidemiological studies demonstrating the nephrotoxicity of different kind of analgesics (reproduced from Elseviers & De Broe,[48] with permission)

Reference	Treatment group	Control group	Definition of minimal abuse[a]	Odds ratios[b]						
				any analgesic	single analgesics[c]			analgesic mixtures		
					any	aspirin (acetylsalicylic acid)	paracetamol (acetaminophen)	any	phenacetin	paracetamol
Case-control studies										
McCredie et al.[38]	80 women with RPN	80 healthy women	3 units/wk for 1y	17.2					18.1	NS
Murray et al.[39]	527 pts with ESRF	1047 hospitalised pts	Almost daily for 30 days	NS						
Sandler et al.[24]	554 pts with newly diagnosed CRF	516 population-based	Daily for 1y	2.79		NS	3.21		7.59	6.9
Pommer et al.[40]	517 pts with ESRF	517 outpatient clinic pts	15 units/mo for 1y	2.44	NS			2.69	4.76	4.06
Morlans et al.[22]	340 pts with ESRF	673 hospitalised pts	15 units/mo for 30 days	2.89		2.54			19.05	
Perneger et al.[12]	716 pts with ESRF	361 population based	Daily for 1y			NS[d]				2.1[d]
Prospective studies[e]										
Dubach et al.[41]	623 healthy women[f]	621 healthy women[f]	NAPAP detected in urine						8.1	
Elseviers & De Broe[37]	200 healthy participants[g]	200 population based[g]	Daily for 1y (overall at least 1000 units)	6.1						

a A 'unit' is described as a single dosage unit of the drug or preparation (e.g. 1 tablet, 1 powder).

b Results are odds ratios showing significant differences between cases and controls.

c Results are obtained after adjustment for the use of other analgesics.

d This analgesic component may have been taken alone or in a mixture.

e Results are relative risks for the development of renal failure during the study period.

f Patients were followed for 10 years.

g Patients were followed for 7 years.

CRF = chronic renal failure; **ESRF** = end-stage renal failure; **NAPAP** = *N*-acetyl-*p*-aminophenol (the main metabolite of phenacetin); **NS** = not significant; **pts** = patients; **RPN** = renal papillary necrosis.

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comparable risk ratios were obtained. However, the small number of patients presenting with signs of renal impairment did not allow the risk of nephrotoxicity with particular types of analgesic preparations to be investigated. In contrast, the case-control design did allow such investigation. However, their contribution to the assessment of different analgesic substances in the development of analgesic nephropathy is limited and controversial.[27,47] For analgesic preparations, particularly for those containing phenacetin or paracetamol, the nephrotoxicity was clearly demonstrated. No consistent results were obtained for single analgesics (table II).

6. Conclusion

There is no doubt concerning the aetiology of 'classic' analgesic nephropathy. It is the result of habitual consumption over several years of analgesic preparations containing 2 analgesics associated with caffeine and/or codeine. In contrast, abuse of single analgesics is seldom described and associated chronic renal lesions are only occasionally reported. The most rational approach to prevention of analgesic nephropathy is the prohibition of over-the-counter sales of analgesic preparations containing centrally acting and dependence-producing agents.

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