Analgesic nephropathy

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CASE PRESENTATION

A 76-year-old white male was referred to the chronic kidney disease clinic at the Brigham and Women's Hospital for evaluation of his kidney impairment of longstanding duration. He was asymptomatic at the time of presentation. His serum creatinine was 2.8 mg/dl and his estimated glomerular filtration rate (GFR) using the abbreviated modification of diet in renal disease study group (MDRD) equation was 24-ml/min/1.73 m^2. The patient's past medical history was remarkable for long-term ingestion of anacin (at the time of consumption, anacin comprised of phenacetin and acetyl salicylic acid), which he bought as an over-the-counter medication for recurrent headaches. Anacin started during his college years and continued for several years (almost 20 years) because no other remedy was found for his recurrent headaches. Although the patient could not recall precisely, he estimated that his average daily consumption of anacin was 2 g/day. Over the past 20 years he had switched to acetaminophen – he estimated that he ingested 3–4 tablets (1.5–2 g) of acetaminophen (single ingredient) each day. He was diagnosed with hypertension in 1977 and initiated on a thiazide diuretic. However, since then the patient has also been treated with atenolol 25 mg once daily, furosemide 40 mg once daily, and losartan 50 mg twice daily. The patient also has a history of gout that was first diagnosed in 1991 and initially managed with colchicine and short courses of sulindac (150 mg twice a day for 5 days) during attacks. However, his gout got progressively worse to the extent of having an attack every 3 weeks and was successfully controlled with initiation of allopurinol 200 mg a day in 1999. In 1991, he was also noted to have mild abnormal kidney function with a serum creatinine of 1.5 mg/dl and an estimated GFR of 53 ml/min/1.73 m^2. His kidney function remained relatively stable for almost a decade. However, since the beginning of 2000 his creatinine gradually rose from 1.5 to 2.8 mg/dl (corresponding to fall in estimated GFR from 53 to 23 ml/min/1.73 m^2).

His current medications include: hydrochlorothiazide 12.5 mg once daily, furosemide 40 mg once daily, atenolol 25 mg once daily, losartan sodium 50 mg twice daily, pantoprazole sodium 40 mg once daily, and a calcium carbonate-based antacid (used on a pro re nata (PRN) basis). Physical examination was unremarkable except for a blood pressure of 144/74 mm Hg. Urinalysis revealed specific gravity of 1.005 and trace protein, but was otherwise negative. His urinary sediment was bland. The differential diagnosis of his chronic kidney disease included analgesic nephropathy, micro or macro vascular kidney disease, and hyperuricemia-associated nephropathy. Computed tomography (CT) scan evaluation of his kidneys without contrast revealed bilateral shrunken and scarred kidneys (Figure 1). There was high attenuation in the papillary regions bilaterally representing mild papillary calcifications consistent with analgesic nephropathy. This CT appearance fits with stage

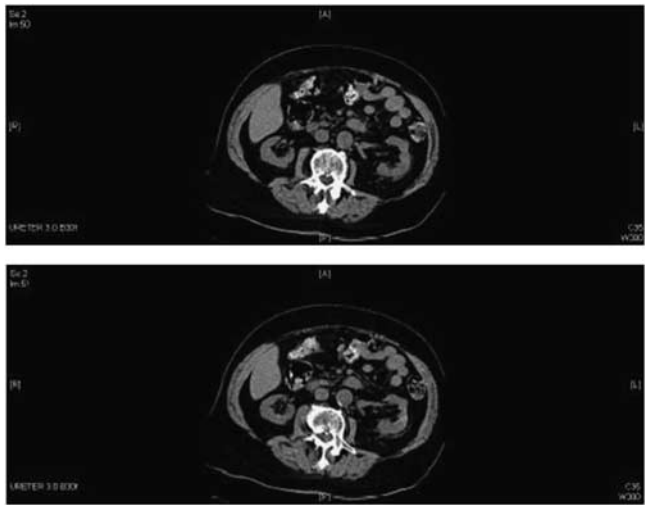

Figure 1 | CT scan of abdomen showing small indented, calcific kidneys (SICK), a finding that is associated with analgesic nephropathy. Using the classification proposed by Elseviers *et al.*[1] this corresponds to stage III disease.

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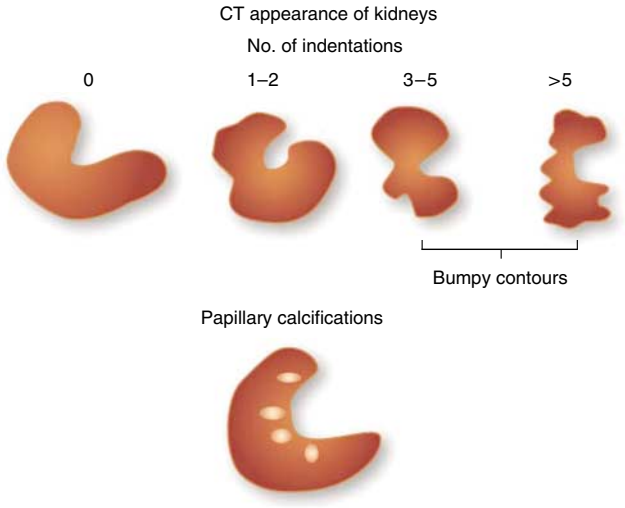

Figure 2 | CT imaging criteria of analgesic nephropathy (adapted from Elseviers *et al*.

Table 1 | Laboratory data

Complete blood count	WBC (10.9 K/μl), HGB (11.7 g/dl), PLT (301 K/μl)
Renal chemistry	Sodium (138 mmol/l), potassium (4.8 mmol/l)
	Chloride (102 mmol/l), total CO_2 (28 mmol/l)
	BUN (61 mg/dl), creatinine (2.4 mg/dl)
	Estimated GFR 28 ml/min
Bone chemistry	Calcium (10.6 mg/dl), phosphate (2.5 mg/dl)
	PTH (30 pg/ml)
Glucose	86 mg/dl
Urine microalbuminuria	6.2 mg/dl
Urine albumin/creatinine ratio	202.6 mg albumin/g creatinine
Urine dipstick	Urine pH 7.0, blood negative, and protein trace
	Specific gravity 1.005
Serum electrophoresis	No abnormal electrophroetic pattern noted

BUN, blood urea nitrogen; HGB, hemoglobin; PLT, platelet; PTH, parathyroid hormone; WBC, white blood cell.

three analgesic nephropathy using the CT imaging criteria proposed by Elseviers *et al.*[1] to diagnose analgesic nephropathy (Figure 2). Laboratory data are shown in Table 1.

PRIMARY DIAGNOSIS

Analgesic nephropathy secondary to chronic multiple analgesic abuse.

CLINICAL FOLLOW-UP

The patient was counseled to avoid analgesics. Although analgesic abuse could have been the primary etiology for the patient's nephrotoxic injury, other causes for nephrotoxic injury, such as gout and hypertension must also be considered, although it is possible that the patient's late onset of hypertension and hyperuricemia could have been to the consequence of his impaired kidney function. The patient's antihypertensive regimen was modified to achieve better control of his blood pressure. At last follow-up, he remained asymptomatic and with a blood pressure of 124/72 mm Hg. He has been started on an angiotensin-converting enzyme inhibitor (lisinopril 10 mg daily). His uric acid level has improved from 9.4 to 4.3 mg/dl with dietary modification and allopurinol therapy. His latest laboratory data reveal kidney function as measured by serum creatinine of 2.4 mg/dl (estimated GFR of 28 ml/min/1.73 m^2) and blood urea nitrogen is 61 mg/dl.

DISCUSSION

The incidence and prevalence of end-stage kidney disease has been steadily increasing throughout the world. Early identification of the modifiable risk factors and risk prevention/reduction is of utmost importance in reversing this trend. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDS) are among the most widely and frequently used drugs, particularly by among those at risk such as the elderly population. Classic analgesics such as acetaminophen (paracetamol), salicylates are commonly used for minor pain syndromes, whereas NSAIDs are considered as effective and well-tolerated first-line drugs for the management of various arthritic and musculoskeletal disorders. Population studies and WHO (World Health Organization) statistics indicate that 10–50% of individuals have a history of musculoskeletal disorders. Easy access to some of these over-the-counter analgesics/combinations by the general public runs the risk of unwarranted and unsupervised chronic intake. Many studies[2,3] have suggested an association between chronic ingestion of analgesics and kidney disease. Because of their widespread use even a small increased risk of kidney disease will have major public health implications.

Definition of analgesic nephropathy

A National Kidney Foundation position paper[4] defines analgesic nephropathy (AN) as 'a disease resulting from the habitual consumption over several years of a mixture containing at least two anti-pyretic analgesics and usually codeine or caffeine. It is characterized by kidney papillary necrosis and chronic interstitial nephritis that leads to insidious onset of progressive kidney failure'. However habitual consumption of some nonopiate analgesics/NSAIDs on their own has been associated with analgesic nephropathy. This association of analgesic consumption with an increased risk of kidney disease is controversial because of criticisms regarding the design and execution of previous positive studies. The majority of previously published papers on analgesic nephropathy report the results from retrospective case control design studies. These studies associating analgesics with kidney disease are susceptible to several sources of bias such as recall bias, selection bias, reverse causality bias, interviewer bias, and (residual) confounding bias. Indeed, a cohort study of analgesic use using data obtained over 14 years from the Physicians' Health Study[5] concluded that moderate analgesic use (acetaminophen, aspirin and other NSAIDS) in healthy men is not associated with increased risk of kidney dysfunction. However, this

study also had limitations largely related to generalizability – because the study population comprised of white male physicians; it is not clear that the results would be applicable to women or minority population.

Analgesics and chronic kidney injury

Until recently, analgesic nephropathy was regarded as a relatively common cause of chronic kidney failure in Australia, some parts of Europe and the United States. However, strict regulations that limited the sale of phenacetin-containing analgesic mixtures and other combined analgesics over the past two decades appear to have resulted in a markedly decreased incidence of AN. Nevertheless, because of its insidious course, phenacetin-induced analgesic nephropathy cases (such as in our patient) may still present clinically. The majority of individuals are diagnosed >45 years of age, suggesting that prolonged, regular ingestion of analgesics could be important as risk factors in the etiology of AN.

Analgesic nephropathy is characterized by kidney papillary necrosis and chronic interstitial nephritis. Both immunological and nonimmunological mechanisms may play a role in the pathogenesis of AN. The early phase changes of AN in humans were first demonstrated in patients with normal kidney function (as measured by serum creatinine) with a history of phenacetin and acetyl salicylic acid consumption – ingestion of a minimum of five tablets a day, for 5 years.[6] In comparison, Burrell *et al.*[7] studied the effect of long-term aspirin and acetaminophen administration in Fischer 344 rats.Histologic lesions seen in experimental-induced AN were similar to those seen in humans. Medullary ischemia seems to be the initiating event. Light and electron microscopy revealed irreversible damage to medullary interstitium, characterized by interstitial cell nuclear degeneration, abnormal interstitial matrix, loss of medullary interstitial cells, and increased collagen. The earliest changes involve sclerosis of vasa recta capillaries and patchy tubular necrosis. Later changes include areas of papillary necrosis and secondary focal segmental glomerulosclerosis, cortical scarring, and interstitial fibrosis. Papillary necrosis may also be the result of reactive metabolic products of the drug or from the accumulation of phospholipids in the papilla. Preexisting analgesic nephropathy[8] and acute pyelonephritis[9] seem to favor the development of NSAID-induced nephrotoxicity.

Diagnosis and screening

The early diagnosis of AN is very important because progressive kidney injury could potentially be halted or even reversed through discontinuation of drug use. Careful questioning of the patient is key but often an accurate history of analgesic consumption is difficult to obtain. The exact duration, frequency, and the number of pills are often forgotten or understated by the patient; hence additional information from a close family member may be useful. Conditions that prompt analgesic use such as recurrent headaches, arthritic pains, or associated symptoms such as history of peptic ulcer disease or ulcer-like symptoms should be enquired and addressed to prevent relapse. Tablets containing opiates or caffeine may cause dependence and would need carefully monitored supportive withdrawal. An early sign of AN is the loss of urinary concentration ability. Hence, patients in need of long-term analgesic/NSAID therapy for conditions such as inflammatory arthritis would benefit from regular screening with urinary dipstick (to assess specific gravity, proteinuria, etc) and serum creatinine measurements. Clinical manifestations of AN are generally nonspecific. It is a slowly progressive form of kidney failure with no urinary sediment or with sterile pyuria or mild proteinuria (<1.5 g/day) on urinalysis. Severe proteinuria that exceeds 3.5 g/day is rare but can be secondary to hemodynamically mediated glomerular injury. Some patients may even have developed advanced kidney failure by the time they present for the first time to a nephrologist.

Although papillary necrosis is present histologically in almost all patients, it can be detected by radiologic imaging only if part or all of the papilla has sloughed.[10] Partial or total papillary necrosis is observed in 25–40% of the patients. Elseviers *et al.*[1] demonstrated that CT scan without contrast has a higher diagnostic performance than other modalities in diagnosing AN.In their European multicenter study, a CT scan observation of decreased kidney length along with either bumpy contours or papillary calcifications in patients with an appropriate analgesic history and mild to moderate kidney impairment (creatinine ranging between 1.5 and4 mg/dl) had a diagnostic sensitivity and specificity of 92 and 100%, respectively, for AN. In end-stage kidney disease patients, these figures were 90%. However, recently, the US National Analgesic Nephropathy Study[11] reported that the constellation of CT findings (small, indented, calcific kidneys (SICK)) is quite infrequent in the US end-stage kidney disease population. Their findings suggested that these CT abnormalities did not occur among a sufficient proportion of heavy analgesic users to justify the use of noncontrast enhanced CT scan as a sensitive tool in the diagnosis of AN.

Role of acetaminophen

Acetaminophen is the primary metabolite of phenacetin. Despite the clearly established association between phenacetin and AN, at present there is insufficient evidence to link habitual acetaminophen use to AN. However, the consistency of the results from existing epidemiological studies and the observed apparent dose–response relationship suggests that such a relationship cannot be excluded.[12] Among 1700 healthy women who participated in Nurses' health study[13] in United States, those consuming >3000 g of acetaminophen had an odds ratio of 2.04 (CI 95% 1.28–3.24) less for a decreased GFR of at least 30 mls/min/1.73 m2 over an 11-year period compared to women consuming 100 g or more. In contrast, Mihatsch *et al.*[14] performed a very careful morphological analysis of 1220 kidneys obtained from 616 adult autopsies between 2000 and 2003 and concluded that classic analgesic nephropathy has disappeared some 20 years after the removal of phenacetin from the analgesic market.

This is despite the fact that mixed analgesics containing acetaminophen, the main metabolite of phenacetin, have continued to be popular. With the currently available evidence acetaminophen remains the nonnarcotic analgesic of choice for occasional use in patients with underlying kidney disease. However, habitual intake of acetaminophen should be discouraged and if indicated medically, a physician should supervise its long-term use.[4]

Role of aspirin

Most studies demonstrate that long-term aspirin monotherapy in therapeutic doses does not cause kidney injury in patients with normal kidney function. However, aspirin should be avoided in patients with impaired kidney function and 'at-risk groups' such as those with volume deplete states, glomerulonephritides, etc. There is no long-term adverse kidney risk with the lower doses of aspirin recommended for prevention of cardiovascular events and stroke.

Role of nonphenacetin-combined analgesics

An *Ad Hoc* Committee of the International Study Group on Analgesics and Nephropathy[15] critically reviewed the currently available data on the relationship between nonphenacetin-combined analgesics and AN. They concluded that at present there is insufficient evidence to link nonphenacetin-combined analgesics with nephropathy. They also observed an absence of any association between the use of caffeine-containing combined nonphenacetin analgesics and kidney injury. However, some studies[16] and experimental data raise concerns of higher risk with these combinations.

Role of NSAIDs

The chronic use of NSAIDs in therapeutic doses is generally safe. However, kidney papillary necrosis and chronic kidney failure can occur in some patients. In contrast to the clearly defined 'at-risk population' for acute kidney failure with NSAIDs, no data delineate their exact risk in inducing papillary necrosis, chronic kidney impairment, and end-stage kidney disease. Exposure to a large cumulative dose of NSAID may lead to chronic kidney disease in some cases. However, the percentage of patients affected is small relative to the number of prescriptions written. As COX-2 inhibitors are relatively new to the analgesic armamentarium, their role in chronic kidney injury is uncertain. Prolonged regular use of NSAIDS should be discouraged but if deemed necessary, it should be closely monitored.

Analgesic syndrome

Analgesic nephropathy is a part of the wider clinical 'analgesic' syndrome, which includes neuropsychiatric, gastrointestinal, hematological, cardiovascular, and dermatological manifestations in addition to the increased risk of developing uroepithelial tumors. Although the major malignancy that has been observed in association with AN is transitional cell carcinoma, other cancers such as renal cell carcinoma and sarcoma has also been reported in the literature. Analgesic-associated tumors are more likely to be multifocal and more malignant than those unrelated to analgesics. These tumors are more likely of renal pelvic origin with frequent accompaniment of renal papillary necrosis and kidney dysfunction. A mean phenacetin consumption of 9.1 kg, a mean exposure time of 17 years, a mean induction time of 22 years, and female sex have been reported as risk factors for these tumors.[17]

CONCLUSION

It is important to highlight the potential adverse effects of analgesic agents on the kidney. Patients who warrant chronic therapy with these agents should be closely monitored for any early signs of kidney injury. Early detection and removal of the offending agent could halt or even reverse analgesic-induced kidney injury. There is a pressing need for multicenter trials to assess the true incidence of this problem and to study the effects of various analgesic agents (alone and in combination) in at-risk populations.

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