Analgesic-associated nephropathy in the West of Scotland: a 12-year observational study

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Abstract

Background. Analgesic-associated nephropathy (AAN) is an important and preventable cause of chronic renal failure (CRF). Although its incidence is falling in some countries, others are witnessing an increase in the number of new cases.

Methods. The aim of this study was to evaluate the natural history of AAN, determine the correlates of the rate of decline in renal function and examine factors conferring an increased risk of death or dialysis in such patients. A prospective observational cohort study of all patients with AAN attending a single-centre was conducted.

Results. Seventy-eight patients (25 male), with at least 24 months of follow-up for analysis, were diagnosed as having AAN over the 10-year period 1989–1999. During follow up, the mean (±SD) rate of change in estimated creatinine clearance (ECC) was −1.2 ml/min/year (± 5.28). By multiple linear regression three variables were found to independently predict the rate of deterioration in ECC; continuing analgesic use (P < 0.001), degree of proteinuria at presentation (P = 0.002) and male sex (P = 0.03). A Cox's model revealed a 6-fold increase in the hazard of reaching the combined end-point of death or dialysis in those patients with AAN who continue analgesics. This was independent of the other two significant risk factors of pre-existing vascular disease (HR 3.93, 1.36–11.29) and ECC at presentation (HR 0.95, 0.91–0.98 per ml/min).

Conclusions. In patients with CRF due to AAN ongoing analgesic use, male gender and increasing proteinuria predict a more rapid decline in renal function. Patients who continue analgesics, those with pre-existing vascular disease and those with more advanced renal impairment at presentation, are at a significantly increased risk of reaching the combined end-point of death or end-stage renal failure requiring dialysis. The design of this study, however, leaves it open to the criticism that selection bias may account for some of its effects, and as with all work on AAN the possible confounding issue of reverse causality is difficult to dismiss.

Keywords: analgesics; analgesic nephropathy; progression; proteinuria

Introduction

Analgesic-associated nephropathy (AAN) is a slowly progressive tubulo-interstitial disease, the histological hallmarks of which are renal papillary necrosis, capillarosclerosis and chronic interstitial nephritis [1]. It was first described in patients using analgesic mixtures containing at least two anti-pyretic agents and caffeine, or codeine, on a daily basis, for at least 3 years. Suspicion that phenacetin was the aetiological agent primarily responsible for papillary necrosis led to its withdrawal in many countries. In the UK access to phenacetin was restricted in 1966. More recently the nephrotoxic potential of commonly used single agent analgesics has been described [2,3] and it has been our practice to diagnose AAN in any patient with renal impairment, a history of habitual analgesic use and the absence of another possible explanation for their renal disease.

Studies of AAN, as well as being beset by epidemiological difficulties, are complicated by the fact that there are no universally accepted diagnostic criteria. Initial descriptions of the condition noted a female preponderance [4] as well as a propensity to develop early vascular disease, hypertension [5] and transitional cell carcinoma of the uroepithelium [6]. Among associated clinico-pathological features were sterile pyuria and impaired urinary acidification. Unfortunately, none of these features are sufficiently sensitive or specific to be of use as diagnostic markers [7]. Multi-centre studies addressing the problem of diagnosis have recommended non-contrast enhanced
CT as the gold standard for demonstration of renal papillary necrosis [7]. However, this has not been widely adopted and AAN therefore remains a diagnosis of exclusion.

The natural history of AAN is poorly understood, particularly since the withdrawal of phenacetin. Although its incidence appears to be declining, in many areas it remains an important, and preventable, cause of end-stage chronic renal failure (ESCRF). The primary aim of this study was to evaluate the natural history of CRF associated with AAN and determine the correlates of the rate of deterioration of renal function in patients with AAN. The secondary aim was to determine which factors were associated with an increase in the risk of either dying or developing ESCRF requiring dialysis during the period of follow up.

Subjects and methods

Glasgow Royal Infirmary is a teaching hospital housing one of two renal units in Glasgow. A computerized database was set up in this unit in 1989 [8]. All in-patients and outpatient referrals seen by staff of the renal unit since then have been entered into this database, and it now contains the records of over 15000 patients. Patients diagnosed as suffering from AAN were selected from the database; their computerized records and case-sheets were examined.

Patients were considered to be suffering from AAN if they had a history of analgesic ingestion on a daily basis (excluding low dose aspirin as an anti-platelet agent) for at least 3 years and no other explanation for their renal impairment could be found. Investigations routinely undertaken to exclude other causes for renal impairment included viral and auto-immune serology, serum immunoelectrophoresis and radiological imaging to exclude anatomical anomalies, renal asymmetry, or changes consistent with reflux nephropathy. In patients with significant proteinuria (≥1 g total proteinuria per 24 h) renal biopsy was considered.

At presentation, demographic data and details of analgesic use were recorded. In addition, the presence or absence of a normal anion gap acidosis (taken as being evidence of impaired urinary acidification) and sterile pyuria at presentation were noted. Degree of proteinuria at presentation, as reflected by a spot urinary albumin:creatinine ratio (ACR) was recorded. Hypertension (as evidenced by treatment with at least one anti-hypertensive, or mean arterial blood pressure of at least 105 mmHg on three consecutive occasions), incidence of pre-existing vascular disease (a definitive vascular event or angiographically proven peripheral vascular disease) and incidence of recurrent urinary tract infections at presentation were documented. Finally, results and type of radiological investigation undertaken in each patient were established. Patients were considered to have small kidneys if bipolar diameter was less than or equal to 8 cm. At presentation all patients were advised to stop all analgesic intake if possible and, at subsequent consultations, a history of ongoing analgesic ingestion, including both over the counter and prescription only preparations, was obtained.

Progression of renal disease

ECC was calculated for each patient, at each clinic visit, using the Cockcroft and Gault formula [9]. The rate of change of ECC in millilitres per minute per year was calculated over the period of follow up, or until death or commencement of renal replacement therapy, using at least five measurements of serum creatinine. This method of calculating progression has been validated by other groups and shown to have advantages over the use of serum creatinine alone or its reciprocal [10,11]. Patients experiencing an episode of acute renal failure (ARF) (defined as a reversible decline in ECC of ≥25%) during follow up were excluded from further analysis.

Statistical analysis

Variables with a skewed distribution were log transformed to approximate normal distribution for statistical analysis. The two groups of patients, those continuing and those stopping analgesics were compared using ANOVA one-way analysis of variance (to compare mean values of continuous variables) and the χ² test (to compare categorical variables). Multiple linear regression was used to determine the correlates of the rate of change of renal function (a continuous dependent variable). Variables associated with reduced patient and renal survival were identified using a Cox proportional hazards model. All models considered clinically relevant interactions between independent variables. For the Cox proportional hazards method nested models were compared using the likelihood ratio test. All statistical analyses were two-sided and a P-value < 0.05 was considered as statistically significant. Statistical analyses were performed using STATA 7.0 software (Stata Corporation, TX, USA).

Results

Demographic data and clinical features

Ninety-four patients (30 male) were diagnosed as having AAN over the 10-year period, 1989–1999. Sixteen patients were excluded from further analysis because they had presented at ESCRF, suffered an episode of ARF during follow up, or had <24 months follow up for analysis. Of the 78 patients in the study, the indication for analgesics was arthritis in 68 patients (osteoarthritis 43, rheumatoid arthritis 11, seronegative polyarthropathies 10 and gouty arthropathy four) and recurrent headaches in two. In eight patients, no organic cause of pain was identified. At presentation, 19 of the 78 patients used non-steroidal anti-inflammatory drugs (NSAIDs), 10 used compound analgesics (a variety of preparations containing paracetamol and an opiate), 24 used NSAIDs and compound analgesics in combination and the remainder (25) used a cocktail of NSAIDs, compound analgesics and paracetamol. No patient gave a history of phenacetin ingestion. During follow up, 27 patients were judged to have ceased all analgesic intake whilst the remaining 51 continued using one or more of the preparations listed above.
Table 1 shows the baseline demographic data and clinical variables in the two groups of patients, separated by history of ongoing analgesic use. Twenty-five of the 78 patients (32%) were male. Only one patient was non-Caucasian. The mean age (±SD) at presentation was 60.7 years (±11.1) and the mean creatinine clearance 41.3 ml/min (±24.7). At presentation, 16 (20.5%) patients had evidence of impaired urinary acidification (renal tubular acidosis), five (6.4%) had sterile pyuria, 62 (79.5%) patients were hypertensive and 49 (63%) had pre-existing vascular disease. Thirty patients (38.5%) were either current or ex-smokers. Kidney size was measured in all patients; seventy-two patients (92%) had a renal ultrasound, while the remaining six (8%) had non-contrast enhanced CT. In addition, 17 (27%) patients had plain radiographs (kidney, ureter and bladder films) and 15 (19%) patients had i.v. pyelograms. Thirty-two (41%) patients had evidence of reduced renal size at presentation. Only four patients underwent percutaneous renal biopsy, and in each case light microscopy revealed evidence of a chronic interstitial nephritis. The median (interquartile range) period of follow up was 58 (41–84) months. During this time 10 patients reached ESRF and 10 patients died, three of whom were already on dialysis (myocardial infarction five, non-urothelial carcinoma two, sepsis one, cause unknown or unrecorded two). The mean rate of change in creatinine clearance during follow up was 1.2 ml/min/year (± 5.28).

Table 2. Correlates of the rate of change in ECC by multiple linear regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient (ml/min/year)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.25</td>
<td>0.16, 2.34</td>
<td>0.026</td>
</tr>
<tr>
<td>ACR (per 10 mg/mmol)</td>
<td>2.99</td>
<td>1.54, 5.80</td>
<td>0.002</td>
</tr>
<tr>
<td>Continued analgesic use</td>
<td>3.53</td>
<td>2.46, 4.60</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. Demographic data and clinical variables in patients with AAN who stopped analgesics as compared with those who continued.

<table>
<thead>
<tr>
<th></th>
<th>Stopped analgesics (n = 27)</th>
<th>Continued analgesics (n = 51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F (n)</td>
<td>8/19</td>
<td>17/34</td>
<td>0.655</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.4 (±12.8)</td>
<td>61.9 (±10)</td>
<td>0.192</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>70 (±43)</td>
<td>64 (±35)</td>
<td>0.537</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>12 (44)</td>
<td>18 (35)</td>
<td>0.468</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>21 (78)</td>
<td>41 (80)</td>
<td>0.786</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>16 (59)</td>
<td>33 (65)</td>
<td>0.636</td>
</tr>
<tr>
<td>Small kidneys, n (%)</td>
<td>10 (37)</td>
<td>22 (43)</td>
<td>0.602</td>
</tr>
<tr>
<td>ECC at presentation (ml/min)</td>
<td>42 (±27)</td>
<td>42 (±24)</td>
<td>0.943</td>
</tr>
<tr>
<td>ACR at presentation (mg/mmol)</td>
<td>34.8 (±56)</td>
<td>43.7 (±88)</td>
<td>0.610</td>
</tr>
<tr>
<td>Change in ECC (ml/min/year)</td>
<td>+1.8 (±6.6)</td>
<td>−2.64 (±3.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or dialysis during follow up</td>
<td>2</td>
<td>15</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Table 2. Correlates of the rate of change in ECC by multiple linear regression analysis

Table 1. Demographic data and clinical variables in patients with AAN who stopped analgesics as compared with those who continued.

Correlates of the rate of loss of renal function

The continuous dependent variable 'rate of change of creatinine clearance' (in ml/min/year) was used for multiple linear regression. No significant interactions were observed between the explanatory variables. Using a backward elimination procedure, we excluded independent variables that did not have a significant effect on the rate of change in creatinine clearance. Three variables were found to be independent predictors of the rate of deterioration of creatinine clearance: male gender (P = 0.03); continued use of analgesics (P < 0.001); and the degree of proteinuria (as represented by the log-transformed ACR, P = 0.002). After adjustment for the other two variables in the model, male patients had an average rate of loss [95% confidence intervals] of creatinine clearance that was 1.25 ml/min/year [0.16, 2.34] greater than that for females; patients who continued analgesics had an average rate of loss of creatinine clearance was 3.53 ml/min/year [2.46, 4.60] greater than that for patients who stopped analgesics; and for every 10 mg/mmol increase in the ACR the average rate of loss [95% confidence intervals] of creatinine clearance increased by 2.99 ml/min/year [1.54, 5.80]. The data are summarized in Table 2.

Variables associated with adverse outcome

The combined end-point of death or dialysis was chosen as the dichotomous dependent variable for the Cox proportional hazards model. Gender, age at presentation, smoking history, presence of pre-existing vascular disease or hypertension, reduced renal volume at presentation, proteinuria and ECC at presentation were selected as independent variables. This was on the basis either of a P-value of < 0.2 on univariate analysis or because previous studies had shown them to have an effect on renal and/or patient survival. No significant interactions were observed between the explanatory variables. Cox regression was initially performed as a single step, but a backwards-stepwise regression model was also performed to ensure the conclusions were robust.
The final model contained three independent variables that significantly increased the hazard of reaching the combined end-point. After adjustment for the other two variables in the model, continued use of analgesics increased the hazard [95% confidence intervals] by a factor of 6.50 [1.40, 30.16] \((P = 0.017)\) and having pre-existing vascular disease by a factor of 3.93 [1.36, 11.29] \((P = 0.011)\). For every 1 ml/min increase in the estimated creatinine clearance (ECC) at presentation, the odds of death or dialysis were reduced by a factor of 0.95 [0.91, 0.98] \((P = 0.005)\). The data are summarized in Table 3.

### Table 3. Hazard ratios for reaching a combined end-point of death or dialysis in patients with AAN by Cox’s Proportional Hazards model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ECC (per ml/min)</td>
<td>0.95</td>
<td>0.91, 0.98</td>
<td>0.005</td>
</tr>
<tr>
<td>Pre-existing vascular disease</td>
<td>3.93</td>
<td>1.36, 11.29</td>
<td>0.011</td>
</tr>
<tr>
<td>Continued analgesic use</td>
<td>6.50</td>
<td>1.4, 30.16</td>
<td>0.017</td>
</tr>
</tbody>
</table>

#### Discussion

The principal findings of this study were that the degree of proteinuria at presentation, the continued use of analgesics and male gender were independent correlates of the rate of deterioration in renal function. Patients who continued to use analgesics were more likely to reach the combined end-point of death or ESRF, as were those with overt vascular disease or with more advanced renal impairment at presentation.

AAN still poses a major public health problem. Although its incidence appears to be falling in much of Europe and Australia [12,13] it is being reported more frequently in Eastern Europe [14–16]. The size of the problem in the developing nations of Asia and Africa is unclear. For nephrologists it represents an important diagnosis because it is one of the few causes of progressive chronic renal impairment, which is entirely avoidable.

The incidence of AAN varies widely within Europe [17] and, while this may reflect social or cultural factors influencing analgesic consumption it may also be accounted for by a difference in the threshold for making the diagnosis. The latter is suggested by a disparity in incidence in bordering European countries and an inverse relationship between the proportion of patients reaching ESRF due to an unknown cause and those with a diagnosis of AAN [17]. Previous studies have shown variation within the UK itself and in 1973 Glasgow was identified as having the highest incidence of AAN [18], a finding that was attributed to the local production and consumption of a proprietary mixture containing phenacetin [4].

The data from this observational study appear to be consistent with the work of others on several counts. The female preponderance is much less marked than it was in some of the earlier descriptions of the condition (2:1 as opposed to 6 or 7:1) [12], the vast majority of patients were taking analgesics for a painful physical condition, and patients tended to be older at presentation. Also, the prevalence of a normal anion gap acidosis and sterile pyuria at presentation were insufficient to render these features useful in diagnosing AAN [17]. The majority of our patients with AAN were hypertensive at presentation, almost two-thirds already suffered from vascular disease, and almost half experienced recurrent urinary tract infections. The three independent predictors of the rate of decline in renal function, to emerge from this study, are male gender, the continuing use of analgesics and proteinuria at presentation. The first is in keeping with other epidemiological data, which suggests that females may be relatively protected in terms of the progression of cardiovascular and renal disease [19]. The reasons for this are unclear but may reflect physiological gender differences in the renin–angiotensin system.

The patients evaluated in this study were divided into those who continued analgesic ingestion and those who ceased taking all analgesics. There were no significant differences between the two groups in terms of racial background, gender, age, ECC or proteinuria at presentation. Furthermore, the proportion of patients in each group with a history of smoking, hypertension and vascular disease was not significantly different. Despite these similarities, the renal function of those who continued to take analgesics declined 3.53 ml/min/year faster than the patients who stopped taking all analgesics. In addition, continuing analgesic use conferred a 6-fold increase in the risk of death or progression to ESRF.

Heavier proteinuria at presentation among the patients in this study was associated with more rapidly progressive renal disease (3 ml/min/year decline in ECC for every 10 mg/mmol rise in ACR). There is general agreement that heavier proteinuria portends a more rapid decline in renal function in a variety of conditions, and a causative link has been proposed [20]. On the other hand, there is an ongoing debate as to the implication of non-phenacetin combined and single agent analgesics in the development and progression of renal impairment and the genesis of AAN. An Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy concluded recently that there was insufficient evidence for an association between non-phenacetin combined analgesics and nephropathy [21]. In addition, recent epidemiological studies concluded that the hypothesis that non-phenacetin compound analgesics play a role in the occurrence of AAN could not be supported [22], and that moderate use of analgesics in a cohort of initially healthy males was not associated with an increased risk of developing renal dysfunction [23]. On the other hand, data from a Swedish case-controlled study have suggested an exacerbating effect on CRF of any cause due to prolonged ingestion of either aspirin or paracetamol [24].
Our study suffers from the same methodological flaws as much of the published work on AAN. Reassuringly, the diagnostic criteria we used identified patients who shared many of the clinical characteristics found in other studies. Nevertheless, the finding of a group of patients who have progressive renal failure and take analgesics is not sufficient to prove that analgesic ingestion is the cause of their renal failure. The improvement in renal function in those who stopped analgesic consumption may imply causality. However, this has been contested. One suggestion is that of reverse causality, an epidemiological phenomenon whereby more rapidly progressive renal impairment causes pain which prompts analgesic ingestion rather than vice versa. This simple idea is difficult, if not impossible to dismiss. It does, however, seem unlikely given that the phenomenon has not been described in individuals with a well-established renal diagnosis such as progressive glomerular or renovascular disease. Alternatively, continued analgesic ingestion may be a confounding factor. For example, patients suffering from an inflammatory arthropathy may be more likely to continue taking analgesics, but their more rapidly progressive renal impairment may relate to the inflammatory milieu rather than any external pharmacological influence. Again, it is difficult to disprove this hypothesis, or indeed to exclude the possibility that some other unidentified factor causes both renal failure and pain requiring the continued use of analgesics. However, a further analysis of the data presented here shows that the rate of progression of renal failure in patients continuing analgesics is not statistically different whether the underlying diagnosis is inflammatory or non-inflammatory arthropathy. This, it could be argued, suggests that the rate of progression of their renal failure owes more to the fact that both continued taking analgesics, than to other factors.

Another potential criticism of this work is that a variety of analgesics and a number of causes of pain (organic and non-organic) have been analysed as a single group. Larger studies would be required in order to tease out the effects of individual analgesic agents. Furthermore, this study involves a relatively small and self-selecting group of patients who were sufficiently motivated to attend hospital clinics regularly, and therefore may not be wholly representative of the wider population. Finally, it is possible that patients who do not follow advice to stop analgesics do not comply with other treatment and that it is their non-compliance with other therapies, which determines their poor outcome.

Despite these flaws the work presented here provides further evidence to support the contention that the continued use of non-phenacetin combined or single agent analgesics is associated with faster progression of renal impairment and an increased risk of reaching a combined end-point of death or ESRF in patients with AAN. It also suggests that heavier proteinuria at presentation, continued analgesic use and male gender predict a more rapid decline in renal function.

Conflict of interest statement. None declared.

References


Received for publication: 25.10.02
Accepted in revised form: 10.3.03