Acute and chronic nephropathy induced by fluindione must be addressed

Gérard Cam, Angèle Tchiango Kwetche, Cécile Vigneau, Pascale Siohan, Guillaume Queffeulou, Philippe Gatault, Eric Laruelle, Alain Crémauld, Philippe Le Cacheux, Nathalie Rioux-Leclercq and Eric Renaudineau

Department of Nephrology, Broussais Hospital, Saint-Malo, France, Department of Nephrology, Pontchaillou Hospital, Rennes, France, Department of Nephrology, Cornouaille Hospital, Quimper, France, Department of Nephrology, Pasteur Hospital, Cherbourg, France, Department of Nephrology, Bretonneau Hospital, Tours, France, Department of Dialysis, AUB medical center, Rennes, France, Department of Dialysis, ECHO medical center, Le Mans, France, Department of Nephrology, Le Foll Hospital, Saint-Brieuc, France and Department of Pathology, Pontchaillou Hospital, Rennes, France

Correspondence and offprint requests to: Eric Renaudineau; E-mail: e.renaudineau@ch-stmalo.fr

Abstract
Background. Among the vitamin K antagonists (VKA), indanedione-derived VKA is suspected to induce an immunological risk. One indanedione-derived VKA, fluindione, is still being used in France. The aim of this study was to evaluate the contribution of VKA to acute and chronic nephritis.

Methods. Twenty-four cases of biopsy proven acute interstitial nephritis (AIN) were retrospectively selected, based on a first intake of VKA within the previous 12 months as well as an increase of at least 50\% of the basal level of serum creatinine. The 24 cases were all treated with fluindione VKA and not with coumarinic VKA.

Results. The subjects studied included 20 men and 4 women, with a mean age of 73.0 ± 9.3 years (range: 44–84). The delay between fluindione introduction and the appearance of an AIN, proven by biopsy when available, was 11.9 ± 6.9 weeks (range: 3–28). Creatinine increased from 123.0 ± 56.4 μmol/L (range: 56–335) at fluindione introduction to 460.7 ± 265.3 μmol/L (range: 109–1200) at the time of AIN discovery. The treatment then consisted of stopping the fluindione and introducing steroids for 21 patients. If a VKA was necessary, fluindione was replaced by a coumarinic VKA. After 6 months, 1 patient died and 15 patients presented severe chronic kidney disease (CKD Stages 4–5). Two patients still required chronic dialysis after 6 months and five patients after 3 years. Patients with pre-existing kidney disease were more prone to develop severe CKD with fluindione.

Conclusion. In this large study, arguments are presented to incriminate fluindione in the induction of acute and chronic nephritis.

Keywords: acute interstitial nephritis; fluindione; vitamin K antagonists
Introduction

Vitamin K antagonists (VKA) are mainly prescribed for the treatment of cardiovascular disease (e.g. arrhythmia, heart valve disease) and venous thromboembolism. Among the 900 000 French people treated with VKA, two-thirds have received fluindione, an indanedione derived VKA, and the remaining one-third have received a coumarinic-derived VKA [1]. Immunoallergic reactions have been proven for phenindione, another indanedione VKA; suspected for fluindione and considered absent, or nearly absent, for coumarinic VKA [2]. Phenindione immune allergic side effects include a high rate of hypersensitivity reactions (1.5–3%) with a predominance of skin lesions, agranulocytosis, thrombocytopenia, hepatitis and for some patients an acute interstitial nephropathy (AIN) [2–4]. Similarly, skin lesions, hepatitis and AIN have been reported as clinical cases or in small series with fluindione intake [5–7].

With fluindione, AIN is diagnosed within one semester usually in association with fever, cutaneous eruption, arthralgias and interstitial pneumopathy. However, information regarding risk factors for the development of kidney disease, and the outcome of these patients is still unknown.

In order to evaluate the contribution of VKA to AIN, we performed a multi-centre retrospective study in eight centres of the French West Society of Nephrology. We selected 24 cases, all with fluindione, that have developed an AIN within 12 months after VKA introduction. The kidney biopsies were reviewed and renal prognosis factors evaluated.

Materials and methods

Cases of suspected VKA-associated AIN were collected from eight nephrology units that belong to the French West Society of Nephrology. Each centre retrospectively interrogated its biopsy database. Selection criteria were: biopsy-proven nephropathy showing interstitial lesions; AIN with a first intake of VKA in <1 year and a creatinine rise of >50%, according to the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria to attest an acute kidney injury [8]. All associated treatments prescribed during the year preceding the AIN were noted. Kidney function was evaluated at the time of the fluindione introduction at the discovery of AIN, at 6 months, 1 year and at 3 years. The kidney function evaluation included serum creatinine, calculation of the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease formula [9] and determination of chronic kidney disease (CKD) classification stage index according to the kidney disease outcomes quality initiative index (K/DOQI) [10]. At the discovery of AIN, proteinuria, leukocyturia and microscopic haematuria were tested using a dipstick. When positive at dipstick, proteinuria was discovered. When positive at dipstick, proteinuria, leucocyturia and microscopic haematuria were tested using a dipstick. When positive at dipstick, proteinuria was discovered. When positive at dipstick, proteinuria, leucocyturia and microscopic haematuria were tested using a dipstick. When positive at dipstick, proteinuria was discovered.

Table 1. Characteristics of the population before fluindione introduction (n = 24)a

<table>
<thead>
<tr>
<th>Demographic data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.0 ± 9.3</td>
</tr>
<tr>
<td>Male/female</td>
<td>20/4</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
</tr>
<tr>
<td>Mean creatinine (µmol/L)</td>
<td>123.0 ± 56.4</td>
</tr>
<tr>
<td>Mean clearance MDRD (mL/min)</td>
<td>61.3 ± 27.6</td>
</tr>
<tr>
<td>CKD Stage (N%)</td>
<td></td>
</tr>
<tr>
<td>CKD Stage 1 (N%)</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>CKD Stage 2 (N%)</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>CKD Stage 3 (N%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>CKD Stage 4 (N%)</td>
<td>2 (8.3%)</td>
</tr>
</tbody>
</table>

*MDRD, Modification of Diet in Renal Disease.

Table 2. Clinical, biologic and histologic data at the time of biopsy (n = 24)

<table>
<thead>
<tr>
<th>Biologic data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cr (µmol/L)</td>
<td>460.7 ± 265.3</td>
</tr>
<tr>
<td>Mean clearance MDRD (mL/min)</td>
<td>16.2 ± 11.3</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Leukocyturia</td>
<td>13 (54.2%)</td>
</tr>
<tr>
<td>Mild proteinuria (0.5–3 g/24 h)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>Nephrotic range proteinuria (&gt;3 g/24 h)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Anaemia (&lt;12 g/dL)</td>
<td>8 (33.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150 000/mL)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Hypereosinophilia (&gt;0.6 × 10⁹/L)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>Moderate cytolysis (transaminases 2–5 N)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Severe cytolysis (transaminases &gt; 5 N)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Hepatic cholestasis (&gt;2 N GGT and/or ALP)</td>
<td>9 (37.5%)</td>
</tr>
</tbody>
</table>

*Cr, serum creatinine; MDRD, Modification of Diet in Renal Disease; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase.

Results

All 24 cases selected, recruited from eight nephrology units, were associated with fluindione intake. The first one was diagnosed in May 1994 and the last one in September 2010. Two patients with interstitial lesions were excluded from this study because they had received fluindione >1 year before the discovery of the AIN. Five other cases addressed were also excluded because they presented a suspected VKA nephropathy but without renal biopsy. No cases of coumarinic-associated AIN were observed. Patients included 20 men and 4 women with a mean age of 73.0 ± 9.3 years (range: 44–84) (Table 1). The indications for fluindione prescription were venous thromboembolisms (9/24), cardiovascular diseases including arrhythmias (13/24) or heart valve diseases (2/24). At the time of the fluindione introduction, serum creatinine basal level was 123.0 ± 56.4 µmol/L (range: 56–335). Fourteen patients exhibited a CKD with 12 patients at CKD Stage 3 and 2 patients at CKD Stage 4. Other drugs with potential immunoallergic side effects prescribed in association with fluindione or in the year preceding the AIN include: diuretics (8/24),
antibiotics (2/24) and proton pump inhibitors (2/24) (Table 1). According to the chronology of the AIN, the contribution of these drugs appeared to be minor.

The diagnosis of AIN was often made in the first 3 months (16/24) and never observed after 7 months with a mean delay of 11.9 ± 6.9 weeks (range: 3–28) after the initiation of treatment. At the time of biopsy, the kidney damage was severe, with a creatinine mean value of 460.7 ± 265.3 μmol/L (range: 109–1200) in the whole population and values >200 μmol/L for 21 patients. Table 2 presents the symptoms and physical signs (fever, arthralgias, rash, interstitial pneumopathy and pruritus), biological and histological data. Renal biopsy revealed interstitial lesions (Figure 1). In addition to typical interstitial lesions, granulomas (2/24) were also present at the biopsy (Figure 2). Glomerular lesions consisted of glomerulosclerosis (6/9), glomerular ischaemic lesions (2/9) and mesangial glomerulonephritis (1/9).

Different therapeutic schemes were used after AIN discovery. Fluindione was removed for all patients and replaced with coumarinic VKAs if necessary (19/24), and a majority of the patients (21/24) were treated with oral steroids. Patients typically received an initial dose of steroids ranging from 0.5 to 1 mg/kg/24 h, which was tapered over a few weeks. Six patients needed acute dialysis during the first 6 months with success in three cases. With the exception of one patient who died prematurely, the changes in the kidney function were evaluated at 6 months and, when available, at 1 year (16 patients) and at 3 years (9 patients) using three parameters: serum creatinine, the GFR index and the CKD stage index as indicated in Table 3.

Four observations can be made from these analyses. Firstly, the removal of fluindione is associated with a reduction of the mean creatinine, thus confirming its contribution (P < 0.01). However, the effect is partial since at 6 months only 5/24 patients have recovered normal kidney function, indicating chronic lesions. Secondly, recovery is not equivalent for all patients and particularly among patients presenting a pre-existing CKD. Thirdly, presence of glomerular lesions on the biopsy predisposes to a more severe CKD (GFR 20.3 ± 8.5 versus 40.5 ± 25.2 mL/min at 6 months, P = 0.03). Although not significant, there was a trend for more severe CKD in the presence of glomerular lesions among pre-existing CKD patients (17.6 ± 6.7 versus 25.2 ± 9 mL/min at 6 months, P = 0.1), suggesting that glomerular lesions may represent an additional risk factor for secondary chronic lesions. Fourthly, severe complications are frequent with two deaths and five patients requiring dialysis at 3 years.

Table 3. Evolution of the kidney function*

<table>
<thead>
<tr>
<th></th>
<th>6 months after AIN</th>
<th>1 year after AIN</th>
<th>3 years after AIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>24</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Mean Cr (μmol/L)</td>
<td>460.7 ± 265.3</td>
<td>271.5 ± 199.1</td>
<td>296.2 ± 231.5</td>
</tr>
<tr>
<td>Mean GFR (mL/min)</td>
<td>16.2 ± 11.3</td>
<td>32.6 ± 22.4</td>
<td>32.5 ± 24.8</td>
</tr>
<tr>
<td>CKD Stage ≤ 2 N (GFR)</td>
<td>5 (68.8)</td>
<td>3 (73.7)</td>
<td>1 (65.0)</td>
</tr>
<tr>
<td>CKD Stage 3 N (GFR)</td>
<td>3 (44.0)</td>
<td>3 (44.3)</td>
<td>1 (32.0)</td>
</tr>
<tr>
<td>CKD Stage 4 N (GFR)</td>
<td>11 (21.6)</td>
<td>6 (22.8)</td>
<td>2 (21.5)</td>
</tr>
<tr>
<td>CKD Stage 5 N (GFR)</td>
<td>4 (9.0)</td>
<td>4 (7.2)</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Missed</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

*Cr, serum creatinine.
Discussion

Immunological nephropathy is a concern with drugs in up to 60–70% of the cases with a particular class effect that involves cellular immunity [11–13]. We need to reiterate that VKA is separated into two classes: the coumarinic and the indanedione. The immunological risk is almost absent when prescribing coumarinic VKA. There has been only two cases of AIN with warfarin [13, 14] and zero cases with acenocoumarol. In contrast, patients administered indanedione VKA are prone to AIN. Numerous cases were reported when using phenindione [2] and few cases with fluindione [5]. As reported in case reports and in the Raynaud’s study that collected seven cases [1], we confirm and clarify several points: the severity of the fluindione–AIN (mean creatinine 460.7 ± 265.3 μmol/L); the short delay in the development of a AIN after fluindione introduction; the frequent association with haematological and liver abnormalities and the presence of related immunological clinical signs. In addition, our study highlights the importance of the kidney biopsy that permits confirmation of interstitial lesions. As previously described, granulomas have been a concern for few patients [1, 15]. In our study, granulomas were present in two patients. These patients have progressed from a pre-existing CKD Stage 3 to CKD Stage 4. The presence of granulomas does not seem to be associated with the renal prognosis in AIN [16]. In contrast, glomerular lesions are associated with a more severe CKD at 6 months. Glomerular lesions are probably present before fluindione introduction since 7/9 cases were detected in patients with a pre-existing CKD. Other factors have been described as being risk factors in the evolution to CKD [17, 18]; however, we failed to detect any association with age, interstitial fibrosis and the duration of acute renal failure. We cannot estimate the rate of this rare complication from this study. We analysed cases collected in the pathology database. These are the most severe cases, the ones addressed to the nephrologists. However, we suspect that less severe cases are more frequent. Another problem is the low report rate, only 11/24 of our cases were reported before this study.

How should we manage patients with fluindione AIN? First of all, fluindione needs to be stopped and a coumarinic VKA should be introduced if necessary, thus permitting partial recovery of the kidney function as observed in our study. Regarding steroids, their utilization remains controversial like in other AIN [12–20]. In 42 patients with drug-induced AIN, Clarkson [21] has not demonstrated any steroid benefit. However, as recently proposed, in order to be effective, steroids have to be started in the first weeks after introduction of the causal treatment [22, 23]. In our population, like in other fluindione–AIN reports [5], a majority of patients (21/24) were treated with steroids with an initial dose of 0.5–1 mg/kg/J. Then, it could be proposed that, for fluindione–AIN with biopsy-proven acute interstitial lesions, steroids are started early after drug withdrawal.

In conclusion, fluindione–AIN is a rare but avoidable complication. As a consequence, coumarinic VKAs have to be considered as a first line treatment particularly in patients presenting pre-existing CKD. If fluindione is chosen, a survey of the creatinine after 2, 4, 8, 12 and 24 weeks has to be performed. A definitive stop of fluindione treatment and a more complete kidney evaluation must be considered if the creatinine level rises during this period. After 6 months, the risk of developing an AIN seems to be minimal.

Acknowledgements. Authors are grateful to Prof Yves Renaudineau (Brest University Medical School, France) and Dr Wesley H. Brooks (H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL) for editorial assistance.

Conflict of interest statement. None declared.

References


Received for publication: 7.3.11; Accepted in revised form: 22.7.11