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The implications of aspirin resistance in renal failure

Sir,

Aspirin resistance is a phenomenon where the expected inhibition of platelet responses is not obtained as evaluated by different biological tests [1]. In addition to non-compliance and other patient-related factors, one of the main reasons for aspirin resistance is its inability to inhibit thromboxane A_2 (TXA_2) biosynthesis *in vivo*.

Many studies have also shown that patients with aspirin resistance are more likely to have an increased rate of recurrence of vascular events [2,3]. Interestingly, in a recent systematic review by Krasopoulos *et al*., the relationship between resistance to aspirin and a history of renal impairment was observed ($P < 0.03$) [4]. This was considered as possibly a chance finding, mainly because of lack of substantial data. However, an abnormality of platelet arachidonic acid metabolism has been well documented to exist in patients with renal impairment [5]. This leads to altered thromboxane synthesis that is a key factor for the development of resistance to aspirin. Initially thought to be due to a 'functional cyclo-oxygenase defect', it is now considered to be due to the increased activity of phospholipase A2 in the platelets of patients with uraemia [5,6].

Thromboxane has also been shown to play an important role in the physiological function of the kidney, and TXA_2 receptors have been shown to exist in renal vasculature and other nephron segments in animal models [7,8]. Various studies have shown that TXA_2 plays a key role in the regulation of renal haemodynamics mainly acting in conjunction with angiotensin II. TXA_2, in addition to angiotensin II and arginine–vasopressin constrict larger vessels within the renal vascular tree via activation of a rho-associated kinase pathway [9]. Thromboxane receptor knockout mice demonstrated reduced renal blood flow and increased filtration fraction and renal vascular resistance, despite normal basal mean arterial blood pressure and glomerular filtration rate [10].

Enhanced production of thromboxane in the kidney has been demonstrated in several diseases including lupus nephritis, ureteral obstruction and nephrotoxic renal injury [11,12,13]. In a normal kidney, the production of TXA_2 and prostaglandin I_2 is well controlled, and the balance between them is important in maintaining homeostasis *in vivo*. In patients with the above conditions, however, TXA_2 synthesis is higher compared to that of prostaglandin I_2. The administration of thromboxane antagonists decreased the severity of these diseases, supporting the important role of thromboxane in their pathogenesis. Kwag *et al*. demonstrated that dietary vitamin E decreased the elevated phospholipase A2 in the kidney tissues of diabetic rats and improved the prostaglandin I_2/TXA_2 balance in the kidney microsomes thus improving vascular complications [14].

Chronic kidney disease is now recognized as an independent risk factor for cardiovascular events, and cardiovascular disease is the major cause of mortality in patients with the disease [15]. Possibly, the increased aspirin resistance in patients with renal failure may indicate that a similar vascular pathology, involving among others thromboxane, exists in these two different vascular beds. More work on the thromboxane pathway is required in the patients with renal impairment, who develop recurrent cardiovascular events, despite being on aspirin. This would pave the way for novel treatments that would help in preventing the progression of both the renal and cardiovascular pathologies.

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Gadolinium-based contrast agents, erythropoietin and nephrogenic systemic fibrosis in patients with end-stage renal failure

Sir,

Nephrogenic systemic fibrosis (NSF) is a rare and debilitating disorder, which affects patients with kidney failure. An association with gadolinium-based contrast agents for magnetic resonance imaging (MRI) was found [1]. However, not all NSF patients had a prior gadolinium exposure [2]. Recently, an association of NSF and the use of erythropoietin was proposed [3]. Our aim was, thus, to investigate the use of gadolinium-based contrast agents and erythropoietin in haemodialysis patients with and without NSF.

Four patients in our dialysis unit developed NSF (between 2002 and 2006). We retrospectively compared those to all other patients requiring chronic haemodialysis ($n = 61$; data collection in August 2007). Besides demographic characteristics, we investigated haemoglobin levels, iron and erythropoietin supplementation, parameters of inflammation, Kt/V and exposure to gadolinium.

Table 1 gives the basic characteristics of patients and controls. There were no differences with regard to age, sex, number of previous kidney transplantations, cumulative time on haemodialysis or primary renal disease. The same was true for Kt/V. The haemoglobin levels were comparable, but NSF patients received higher doses of erythropoietin (331.1 $\pm$ 215.1 versus 133.3 $\pm$ 99.5 U/week/kg body weight; $P < 0.05$). In the NSF group, 4/4 of the patients received erythropoietin and in the control group 53/61 ($P > 0.05$).

In the NSF group, on average, more contrast enhanced MRIs had been performed [3.0 $\pm$ 1.2 per patient (range 2–4) versus 1.8 $\pm$ 2.0 per patient (range 0–10); the mean dose contrast agent 12.6 $\pm$ 5.4 versus 11.6 $\pm$ 4.6 mmol/MRI]. In the control group, the following contrast agents were used: gadopentetate dimeglumine 94 times, gadodiamide 9 times, gadobutrol 4 times and gadobenate dimeglumine once. In the NSF group, gadopentetate dimeglumine and gadodiamide were used six times each. The cumulative dose of contrast agent was higher in the NSF group (0.57 ± 0.14 versus 0.29 ± 0.37 mmol/kg body weight; $P < 0.05$). In the NSF group, the time from the last administration of a contrast agent to the first symptoms was 2 weeks till 5 months. Comparing those patients with a minimum of two MRIs (as this is the minimum number in the NSF group) patients in the NSF group, again, received higher doses of erythropoietin (331.1 $\pm$ 215.1 versus 128.1 $\pm$ 215.1 U/week/kg body weight; $P < 0.05$).

There is growing evidence for a pathogenic role of gadolinium ions as causing agents in the development of NSF [1]. However, not all patients with NSF have been exposed to gadolinum-containing contrast agents [2,5,6]. There seems to be a reasonable likelihood of additional (co-)triggers, which may-–alone or in combinations-–play a role in the pathogenesis of NSF. In some studies, an association between erythropoietin and NSF [3,7,8] could be found, while not in others [6,9]. One of the cardinal features of NSF is the presence of CD34+ fibrocytes [10]. These cells resemble bone marrow-derived progenitors. One hypothesis says that erythropoietin could drive the development of NSF by increasing the number of circulating haematopoietic stem cells and endothelial progenitor cells, thereby increasing the pool of CD34+ cells. These cells finally may enter the tissue and enhance the fibrotic process. Alternatively, the higher dosage might also reflect erythropoietin resistance in the presence of chronic inflammation, making higher dosages necessary to achieve equal levels of haemoglobin [3,4,11].

The findings of our study have to be interpreted cautiously. The number of NSF patients is small and whether the association with erythropoietin is causative or reflects erythropoietin resistance cannot be answered. However, even if gadolinium seems to be the major culprit in the development of NSF, there is no final proof and a number of questions remain open. The search for (co-)triggers in the development of NSF is strongly warranted. This is especially true in light of limited treatment options of this disabling disease.

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