RIG-I in diseased human kidneys by an immunohistochemical technique.

In this study, it appeared that the amount of immunohistochemically detectable RIG-I was related to the severity of the glomerular lesions, such as that of leucocyte exudation into the glomeruli, in the specimens obtained from cases with active lupus nephritis. Two cases, with severe histological changes and a very high histological activity index, showed significantly more intense immunostaining for RIG-I. Furthermore, the staining intensity decreased in parallel with the improvement of the histological activity index at the second biopsy. These observations suggest that the expression of RIG-I in lupus nephritis could be useful as a parameter for reflecting the histological activity and severity of the renal disease.

In conclusion, we demonstrated that RIG-I expression occurs at levels detectable by indirect immunofluorescence examination, and that the intensity of its expression is correlated with the histological activity index in cases of lupus nephritis. The mechanisms by which RIG-I mediates the inflammatory and immunological processes involved in lupus nephritis still remain to be determined, and must be addressed in future studies.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfm175

Advance Access publication 3 April 2007

Cinacalcet modifies the pH of solutions in vitro: possible implications for gastro-intestinal side effects in vivo

Sir,
The US-based Federal Drug Agency (FDA) and the European Medicines Agency have approved the use of cinacalcet HCl for the treatment of secondary hyperparathyroidism in patients on dialysis, and in those with parathyroid carcinoma [1]. Cinacalcet is effective and, overall, well tolerated [2]. However, in clinical trials, it has been observed that certain patients on cinacalcet have episodes of hypocalcaemia (1.4% of patients), nausea (~31%) and vomiting (~27%), much more than in patients receiving a placebo [3,4]. Gastrointestinal intolerance, with vomiting in particular, has been found to be dose-related, and is the most common reason for drug discontinuation. Moreover, cinacalcet therapy can exacerbate oesophago-gastro-duodenal disease in ESRD patients, gastric fluid pH ranging from acid excess to achlorhydria.

The aim of our study was to clarify whether the in vitro dissolution of commercially available cinacalcet causes medium pH variations in solutions with different basal proton concentrations, simulating gastric, duodenal and intestinal pH, respectively.

Cinacalcet 60 mg (AMGEN Europe B.V.) was dissolved following the USP dissolution II paddle method at a rotation speed of 50 r.p.m. in 900 ml of dissolution medium at a stable temperature of 37 ± 0.01°C, maintained by a Haake cryostat.

pH variations were determined by a pH-meter in solutions at different pH, corresponding to the fluids of different gastro-intestinal segments: 1.90, 5.90, 7.51 [5]. The dissolution profile was obtained from the change of the area under the spectral profile observed using spectrophotometric UV measurements in the 230–320 nm range, while the profile of the change of pH was obtained by introducing a pH-meter into the solutions. Variations in pH were graphically reproduced using Prism Statistical software (version 4.00; Graphpad, San Diego, CA, USA). Each value represents the average of acquisition replicates of nine measurements.

Dissolution of 60 mg of cinacalcet in an acid pH (1.90) medium did not modify the acidity of the solution, whereas in an alkaline solution, the drug induced a rapid increase in acidity (from pH 7.50 to pH 6.70). Finally, the change in proton concentration of the solution at pH 5.90, simulating the duodenal environment, is of particular interest, since it changed towards significant acidity (5.30) Fig.1. Notably, pharmacokinetic findings showed that the absorption of cinacalcet is dominantly duodenal. The observed pH changes in vitro would suggest that, in vivo, orally ingested cinacalcet might rapidly transform alkaline gastrointestinal fluids into acid fluids. This could be of clinical relevance in ESRD patients who ingest the drug.

The acidifying action of cinacalcet derives from its chemical composition, a phenylalkylamine compound with a fluorine radical. We used trehalose in order to modulate the acidifying effect of cinacalcet. This disaccharide with a fluorine radical. We used trehalose in order to modulate the acidifying effect of cinacalcet. This disaccharide is used with increasing frequency to stabilize pharmaceutical products, and it has a significant effect on H-binding structures [6]. The addition of trehalose together with cinacalcet 60 mg to the medium at a pH of 5.9 allowed the pH value to remain stable, while the drug dissolved rapidly and completely.

In addition to this in vitro experiment, we performed 24-h oesophago-gastro-duodenal pH measurement in a 56-year-old Helicobacter Pylori-negative male haemodialysis patient, who was receiving a proton pump inhibitor. He was given cinacalcet because of secondary hyperparathyroidism. After administration of the drug, a 5cm electrode was positioned at the oesophago-gastro-duodenal juncure and another in the stomach, to evaluate pH changes. The patient took three meals (breakfast, lunch and dinner). He was in an upright position for 14 h 30 min and in a supine position for 9 h 30 min. Both after breakfast and lunch the patient

took a dose of cinacalcet orally. At 13.00 h, he had an episode of vomiting preceded by epigastric pain, which coincided with persistent acid reflux.

For the 24-h observation period, the patient had 208 episodes of acidic gastro-oesophageal reflux (pH < 4), 186 of which occurred in the upright and 22 in the supine position. There were three episodes of acid reflux that lasted more than 5 min, the most persistent episode lasting 14 min (after cinacalcet ingestion). Oesophageal acid exposure over 24 h was 7.1% (normal value 4.2%), with 11.2% during upright position, and 0.7% during supine position. These pH measurements demonstrate that cinacalcet can increase the degree of exposure to acid, and induce the oesophageal gastric reflux with its accompanying symptoms.

During a second 24-h period, the oral administration of trehalose to the patient together with 60 mg cinacalcet on the same diet, led to a reduction in the acidic effects, with a marked reduction of side effects, and only 49 episodes of gastric reflux (pH < 4). No episodes of acid reflux longer than 5 min were recorded, the longest episode lasting 5 min after the administration of trehalose and cinacalcet.

In conclusion, cinacalcet appears to be able to enhance the acidification of gastrointestinal fluids. The effect is more marked in alkaline than in acid solutions. This could be of particular importance in uraemic patients, in whom gastrointestinal pH values are often abnormal. The association between the drug and the disaccharide trehalose that binds the proton loads responsible for acidification, could be a simple and economic solution for patients with gastrointestinal symptoms in response to cinacalcet administration.

Conflict of interest statement. None declared.

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Interstitial nephritis in a patient taking sorafenib

Sir,
Sorafenib (Nexavar, Bayer-Onyx) is an oral multi-targeted kinase recently approved by the FDA for the treatment of advanced renal cell cancer (RCC). This treatment has been associated with an increased number of adverse events, as compared with placebo [1], but no renal failure has been noted. We report on a patient who developed a renal insufficiency related to acute interstitial nephritis (AIN) while taking sorafenib.

A 66-year-old male presented with a 2-day history of nausea and facial erythema. This episode began approximately 10 days after taking 200 mg of sorafenib, given orally twice daily for metastatic RCC. This treatment was prescribed after the failure of an 8-month sunitinib treatment (stopped one month previously). His past medical history included nephrectomy, hypertension and chronic renal failure related to focal segmental glomerulosclerosis. Physical examination revealed a painful erythematous rash on the face, upper trunk and proximal upper limbs as well as angioedema of the tongue. Body temperature was 38.5°C. Blood pressure rose from 140/90 to 170/100 mm Hg before and after sorafenib initiation. Urinalysis revealed 2+ protein and 3+ blood; the urine sediment contained dysmorphic red cells and white-cell casts. Laboratory data on admission included the following: leucocytes 11,450/mm³ with eosinophils 916/mm³ (normal < 700), urine proteins (from 0.7 to 240 g of protein in a 24-h collection), 70 leucocytes per high-power field, 20 erythrocytes per high-power field and negative urinary cultures. Serum creatinine concentration rose from 3.6 to 4.5 mg/dl (400 μmol/l). Renal biopsy revealed a focal AIN (Figure 1) associated with polynuclear infiltration in some glomerular capillary wall in the setting of chronic glomerulosclerosis.

The patient was treated with oral prednisone at a dose of 0.5 mg/kg for 4 weeks, followed by rapid tapering. Serum creatinine level fell to 3.4 mg/dl over the next 2 weeks without the need for dialysis and the urinary leukocytes disappeared despite maintenance of sorafenib therapy at 200 mg daily.

Sorafenib prolongs progression-free survival in patients with metastatic RCC in second-line therapy after cytokine failure. In the phase 3 study against placebo, skin toxicity and diarrhoea were the main limiting toxicities reported. Erythema of the face, scalp and upper thorax were reported (40% and 16% with sorafenib and placebo, respectively) [1].

In large retrospective series, AIN represented 2–3% of all native renal biopsies [2], was drug-related in 92% of cases [3], and is associated with a generalized cutaneous rash in 25–30% [2,4].

In this report, we cannot totally eliminate the role of sunitinib in the occurrence of this nephrotoxicity, although that possibility seems unlikely in view of the temporal relation with the use of sorafenib.

This case of AIN should serve as a warning that the use of sorafenib may be associated with renal injury. We suggest careful monitoring for urinalysis and serum creatinine of patients receiving sorafenib, especially those with dermatologic events.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfm199

Fig. 1. Interstitial inflammation by lymphocytes and few plasma cells leading to a focal tubulointerstitial nephritis (A) Masson’s trichrome; original magnification ×200. The lymphocytes population is polymorphous with T and B cells; immunohistochemical staining CD3 (B) and CD20 (C).