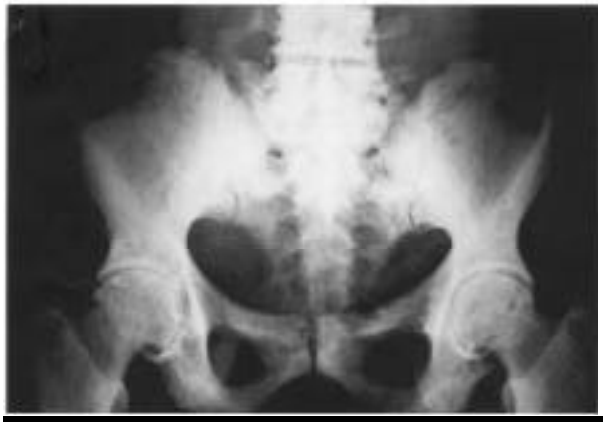

Fig. 1. X-rays of the pelvis: marked osteosclerosis without changes in size.

nosis of a sacroiliitis. The skull, cervical and thoracal spine, upper and lower limbs showed normal bones and moderate osteoarthritic changes. Looser's zones have not been identified. Measurements of bone mineral density (DEXA) revealed a T-score of the lumbar spine (L2-L4) of +3.9 and of the femoral neck of -2.2. Routine laboratory parameters and biochemical markers of bone metabolism, including serum calcium, inorganic phosphate, total alkaline phosphatase, bone specific alkaline phosphatase, 25-hydroxyvitamin D, 1.25-dihydroxyvitamin D, osteocalcin, intact PTH, kreatinin and phosphate clearence were within normal limits. Testing for HLA-B27 was negative. Only one time (due to bone biopsy) there was a slight increase of total alkaline phosphatase. Histological examination of an iliac crest bone biopsy showed thickening of the cortices, increased trabecular bone with broad seams of unmineralized osteoid due to osteomalacia.

The radiologic, densitometric, laboratory and histologic findings in the patient presented herein are compatible with AAO (Fig. 1). The patient was successfully treated with NSAID.

AAO is often asymptomatic and could also be detected in elderly women without any features of sacroiliitis or abnormal bone metabolism. The differential diagnosis of the radiological appearence included bone metastases, systemic mastocytosis, Paget's disease of bone, osteopetrosis, fluorosis, myelofibrosis, fibrogenesis imperfecta ossium, beryllium-, strontium-, cadmium-, plumbum-poisoning, hyperparathyroidism and renal osteodystrophy. For diagnosis other relevant diseases of bone should be excluded by bone biopsy and histologic examination.

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Haemorrhagic gastritis and bleeding following rofecoxib administration

Sirs,

Selective inhibitors of cyclooxygenase-2 (COX-2) have been clinically developed to achieve therapeutic effects comparable to those of conventional non-steroidal anti-inflammatory drugs (NSAIDs), without causing damage to the digestive mucosa (1). Here we describe a case of gastrointestinal bleeding which occurred after treatment with the selective COX-2 inhibitor rofecoxib, reported to us by Pharmasearch, an Italian network of general practitioners for the spontaneous reporting of adverse drug reactions.

A 76-year-old woman referred to her family physician for the onset of severe epigastric pain, associated with the emission of dark stools and one episode of coffee-ground emesis. She was affected by bilateral gonarthrosis, diffuse osteoarthritis, and low back pain. Rofecoxib 25 mg/day had been prescribed by her physician to treat a flare of osteoarthritic pain. The patient assumed rofecoxib for 20 days without complaining of digestive symptoms and then, once the pain was relieved, the treatment was suspended. A few days after rofecoxib withdrawal, the patient developed epigastric pain accompanied by the emission of dark stools and one episode of coffee-ground emesis. After neglecting such disturbances for about one month, the patient referred her symptoms to the physician during a visit scheduled to review the results of routine laboratory examinations (all values being normal). The physician prescribed lansoprazole 60 mg/day, and requested an upper digestive endoscopy. The endoscopic examination revealed haemorrhagic-erosive gastritis, with the body and antrum mucosa being extensively affected by both flat and protruding erosions, and with broad intervening areas of intramucosal bleeding. The patient reported no tobacco or alcohol consumption, but referred previous digestive disturbances in concomitance with NSAID use. The patient's medical history did not indicate documented episodes of peptic ulcer or dyspepsia. The patient had been having treatment with the antiepileptic drug carbamazepine 400 mg/day, for 12 years, following the surgical removal of a meningioma. Lansoprazole treatment for two months fully relieved the patient's digestive symptoms. The application of Naranjo algorithm (2) to the present case allowed to rank as 'probable'the causal link between rofecoxib administration and the occurrence of adverse digestive events. A putative interaction with carbamazepine was taken also into account to explain the above symtoms, but there is no evidence in literature to support such a hypothesis.

Based on pharmacoepidemiological data, this patient can be considered at increased risk for NSAID-induced digestive toxicity, due to sex, age and history of NSAID-induced digestive toxicity (3,4), and therefore she is likely to have experienced an episode of upper digestive bleeding following treatment with a COX-2 inhibitor. Although COX-2-inhibitors appear to be safer than conventional NSAIDs in controlled trials (5), treatments with the former drugs have been associated with upper gastrointestinal complications in post-marketing studies (6). There is also recent evidence of selective prescription of COX-2 inhibitors

(channelling) to patients with high risk for NSAID-induced gastrointestinal injury, with consequent increments in the prevalence of adverse digestive events (7). The prescription of COX-2 inhibitors to patients without risk for NSAID-induced digestive toxicity thus appears to be feasible in conditions of relative safety, and protective therapy with proton pump inhibitors or prostaglandin analogues is not usually recommended (8). However, it remains unclear whether protection of the digestive mucosa should be ensured when prescribing COX-2 inhibitors to patients with specific risk factors. Recent studies have partly challenged previous assumptions underlying the therapeutic rationale for development of selective COX-2 inhibitors. The constitutive expression of COX-2 has been demonstrated in normal digestive tissues, and this isoform can be further induced in proximity of ulcerative lesions, where it might contribute to repairing processes (9). As a consequence, the pharmacological blockade of COX-2 could hamper the mechanisms underlying ulcer healing (10). Overall, COX-2 inhibitors should be prescribed with caution to patients with specific risk factors for adverse digestive events, and revisions of current guidelines should be undertaken to allow a safer use of these drugs in all patient subgroups.

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Circadian profile of serum melatonin in patients with systemic sclerosis

Sirs,

Melatonin (MT) is secreted by the pineal gland, and is believed to be transduction of light exposure into the neuroendocrine system. A circadian rhythm of MT secretion is related to light-darkness exposure. MT modulates immune and endocrine functions (1).

Systemic sclerosis (SSc) is a disease characterized by immune, vascular and fibrotic abnormalities (2,3). *In vitro* studies revealed that low doses of MTexerted a stimulatory effect on fibroblast growth (4). SSc patients have sleep disturbances or depression, the disorders related to MT secretion (5). MT is known as free radical scavenger, and an increased level of free radicals in SSc patients was reported (6).

Nine women with definite SSc, aged 33.7 ± 1.9 yr, and 8 age-matched healthy women were investigated. All investigated subjects were kept at normal light exposure from 6.00 to 22.00. Serum MT was determined with direct RIAmethod.

A circadian rhythm of serum MTwas found in all investigated individuals. MT levels were lower in the SSc patients than in the controls, and AUC during 24 hr as well as during the light or dark period were significantly lower. Maximal MT values were found between 2.00-4.00. Mesor which reflected mean hormone level was shown to be 11.4 pg/ml in the SSc patients and 37.3 pg/ml in the controls (Table I).

The obtained data indicate for suppression of MTsecretion in the SSc patients without alterations in its circadian rhythm. Low MT may be primary or related to other endocrine abnormalities phenomenon (7-10). Further studies are needed.

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Table I. Circadian profile of serum melatonin in patients with systemic sclerosis and healthy controls.

Serum melatonin (pg/ml)	Systemic sclerosis	Healthy controls
8.00 hr	14.68 ± 5.57	33.36 ± 6.92*
12.00 hr	11.72 ± 3.26	30.63 ± 8.40*
16.00 hr	11.22 ± 3.53	28.57 ± 6.31*
20.00 hr	8.68 ± 3.26	28.63 ± 8.65*
22.00 hr	18.18 ± 4.63	42.52 ± 7.34*
24.00 hr	41.19 ± 5.10	75.11 ± 14.81*
02.00 hr	65.86 ± 6.84	89.53 ± 16.16*
04.00 hr	45.68 ± 4.21	62.99 ± 15.98*
06.00 hr	19.43 ± 4.23	36.56 ± 6.29*
08.00 hr	14.10 ± 4.89	34.00 ± 6.50*
AUC 24 hr-period	542.63 ± 45.77	1039.51 ± 189.16*
AUC light period	199.56 ± 28.29	505.17 ± 112.89*
AUC dark period	343.07 ± 31.43	534.34 ± 96.33*
Mesor (pg/ml)	11.4 ± 11.3	37.3 ± 14.5
Amplitude (pg/ml)	23.7 ± 16.2	24.3 ± 14.1
Acrophase (hr)	03 : 02	03 : 18

Statistical significance of the difference between the patients and controls. * $p < 0.001$