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Letter to the Editors

Periprandial administration of inhaled iloprost: a risk factor for digestive bleeding?

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The role of inhaled iloprost should be suspected in cases of gastro-intestinal haemorrhage in patients suffering from pulmonary hypertension (PH) receiving this treatment, and the way the drug is administered should possibly be changed.

Clinical, functional and haemodynamic deterioration of systemic scleroderma-PH in a 73-year-old Caucasian woman without any other past medical history, led to the introduction of aerosolized iloprost 5 μg six times a day in addition to her existing treatment of sitaxentan 100 mg once daily, sildenafil 20 mg three times daily, furosemide 40 mg once daily, bromazepam 6 mg one to two times daily, calcium 1000 mg once daily, cholecalciferol 880 IU once daily, monosodic alendronate 70 mg weekly, fluindione 20 mg once daily with an international normalized ratio (INR) maintained between 2 and 3. In the past, she had had occasional melaena, once a month, generally the day following alendronate ingestion. Two months after beginning aerosolized iloprost, the frequency of her melaena increased, becoming continuous, after each aerosolization (INR = 2.18). An oesogastroduodenal endoscopy revealed digestive angiomatosis, and the hypothesis that iloprost could play a role in causing this lesion to bleed was raised. As reassessment of pulmonary hypertension suggested the benefit of inhaled iloprost, it was decided to reduce the regimen to five aerosols a day, avoiding the first post-prandial hour. The frequency of melaena decreased and abdominal meteorism stopped completely. Reducing the dose of aerosols did not have any effect on the PH at the next reassessment.

In a 79-year-old Caucasian man with a past medical history of ischaemic cardiomyopathy, inhaled iloprost aerosol 5 μg six times a day was initiated following deterioration of a PH secondary to a chronic obstructive pulmonary disease, in association with previous treatment with sildenafil 20 mg three times daily, bosentan 125 mg two times daily, fluindione 20 mg once daily (INR between 2 and 3 throughout follow-up), furosemide 40 mg once daily, amiodarone 200 mg once daily, pravastatin 40 mg once daily, ramipril 5 mg once daily, clopidogrel 75 mg once daily, tiotropium bromide 1 inhalation day^{-1}, molsidomine 2 mg three times daily and potassium chloride 600 mg day^{-1}.

One month earlier, anaemia with iron deficiency had been diagnosed and treated by blood transfusion and ferrous sulphate supplements (80 mg two times daily). Oesogastroduodenal endoscopy had revealed millimetric bleeding angiodysplasias in the duodenal cap, which had been treated by argon plasma coagulation. Four months after beginning inhaled iloprost, haemoglobinaemia was 85 g l^{-1} with iterative digestive haemorrhages requiring several blood transfusions, despite ongoing ferrous supplementation. A colonoscopy found a 3 mm caecal angiodysplasia and two colic polyps requiring argon plasma coagulation therapy and polypectomy. In spite of this digestive procedure, gastro-intestinal haemorrhage continued and consequently clopidogrel was stopped and iloprost reduced to 5 aerosols a day, avoiding the immediate post-prandial period. There was no recurrence of digestive bleeding and haemoglobin stabilized. At the next reassessment, there had been no worsening of PH.

These two cases suggest a possible link between digestive haemorrhage and iloprost aerosols. There was a temporal relationship between inhalation of iloprost and the onset or worsening of bleeding, and between the reduced dose of iloprost inhalation and improvement of bleeding symptoms. The digestive haemorrhage did not recur after the iloprost dosage was reduced and inhalation was avoided after meals. The role of fluindione can be excluded because the INR did not increase and because bleeding symptoms improved despite the continuation of fluindione treatment. In the second patient, stopping clopidogrel may have had a beneficial effect on gastro-intestinal haemorrhage, but the symptoms worsened when iloprost was started, requiring blood transfusion. The role of other drugs can be ruled out as bleeding symptoms improved despite the continuation of these drugs. Neither of these patients had any history of liver disease.

The evidence for the effect of inhaled iloprost on digestive bleeding is strong and possibly multifactorial. Iloprost is an analogue of epoprostenol. Besides its vasodilatory effect, it inhibits platelet function in a dose-related manner and platelet aggregability returns to baseline levels after the end of the infusion [1]. Because its absolute bioavailability is approximately 80% [2], inhaled iloprost may induce sufficiently high serum concentrations to produce adverse systemic effects. Splanchnic blood flow increases after iloprost administration [3], which could promote the bleeding of an angioma. This pharmacodynamic effect could also explain why bleeding symptoms improved when iloprost was no longer inhaled close to meals. It is possible that part of the aerosolized iloprost is swallowed rather than truly inhaled and could have a direct action on the digestive cell wall. Prostaglandins inhibit secretion of histamine and pancreastatin by enterochromaffin-like cells of the gastric epithelium and therefore decrease gastric acidity, making the hypothesis that digestive haemorrhage is related to gastro-duodenal ulcers highly improbable [4].

In conclusion, these observations suggest that patients with a risk of digestive bleeding should avoid inhaled aerosols during peri-prandial periods as far as possible, and that patients with a history of digestive bleeding should be monitored clinically and biologically during the months following the introduction of inhaled iloprost.

Competing interests

There are no competing interests to declare.

REFERENCES

1 Grant SM, Goa KL. Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. Drugs 1992; 43: 889–924.

2 Olschewski H, Rohde B, Behr J, Ewert R, Gessler T, Ghofrani HA, Schmehl T. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. Chest 2003; 124: 1294–304.

3 Kiefer P, Tugtekin I, Wiedeck H, Bracht H, Vogt J, Wachter U, Weiss M, Altin C, Georgieff M, Radermacher P. Hepato-splanchnic metabolic effects of the stable prostacyclin analogue iloprost in patients with septic shock. Intensive Care Med 2001; 27: 1179–86.

4 Lindstrom E, Hakanson R. Prostaglandins inhibit secretion of histamine and pancreastatin from isolated rat stomach ECL cells. Br J Pharmacol 1998; 124: 1307–13.

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