CASE REPORT

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Unexpected Sudden Death During Propranolol Therapy in a Patient with Mild Mesenteric Venous Myointimal Hyperplasia

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ABSTRACT: Propranolol, a beta-adrenergic blocking agent commonly used in the treatment of hypertension, decreases mesenteric blood flow during exercise, at rest, and in cirrhosis. Widespread idiopathic myointimal hyperplasia of mesenteric veins produces intestinal ischemia in otherwise healthy individuals. This report describes a 42-year-old woman who died suddenly and unexpectedly while attending a ball game. She had hypertension treated with propranolol and no other clinically apparent disorders. Autopsy revealed mild mesenteric venous myointimal hyperplasia and segmental jejunal infarction. Recent clinical and experimental studies are used to propose possible mechanisms for this death which combine the effects of propranolol and mesenteric venous myointimal hyperplasia.

KEYWORDS: forensic science, forensic pathology, propranolol, venous myointimal hyperplasia, sudden death, jejunal infarction

Propranolol is a beta-adrenergic blocking agent commonly used in the treatment of hypertension. Recent physiological studies have shown decreased mesenteric blood flow in patients taking propranolol during exercise (1), at rest (2), and in cirrhosis (3). Idiopathic venous myointimal hyperplasia has recently been reported in otherwise healthy individuals (4). In this entity, intestinal ischemia is the presenting syndrome in patients showing pathological changes of venous myointimal hyperplasia (4). This report concerns an unexpected sudden death due to segmental jejunal infarction in a patient taking propranolol for hypertension and showing mild myointimal hyperplasia of mesenteric venules.

Case Report

The patient, a 42-year-old woman, had hypertension controlled with propranolol. On the day of her death, she was attending a baseball game when she suddenly complained of chest pain and suffered a seizure in the baseball stadium. She became unresponsive and was rushed to the emergency room of a hospital where she was pronounced dead shortly after arrival. Autopsy showed an acute segmental infarction of the jejunum associated with a small purulent peritoneal effusion. Exploration of the superior and inferior mesenteric arteries showed no obstruction. The jejunum was blackened and foul smelling in several disjoint regions with grossly normal areas between. The heart weighed 400 g and the right atrium was dilated. The coronary arteries showed no sclerosis. Edema and congestion were present in both lungs. The liver and spleen were congested. The esophagus, stomach and colon were normal. The kidneys, urinary bladder, adrenal glands, reproductive organs, thyroid and brain were all normal. Microscopic examination of the necrotic areas of the jejunum showed full thickness necrosis. There was loss of the mucosal layer and separation of the inner and outer portions of the muscularis externa (Fig. 1 inset). Multiple sections of the mesentery showed no vascular thrombosis, but an occasional venule showed medial muscular hyperplasia with partial obstruction of the lumen (Fig. 1).

Discussion

The histological findings in the mesenteric venous system are similar to those described by Genta and Haggitt (4). In their four cases, venous myointimal hyperplasia was so widespread that it was the sole cause of intestinal ischemia. In contrast, the case reported here shows less widespread myointimal hyperplasia, and by itself does not cause disease. Thus, one might postulate that an extra factor is needed to cause the ischemic infarction seen at autopsy. The effect of propranolol on the mesenteric circulation, also by itself not severe enough to cause necrosis of the small intestine, could be such a factor.

The sudden nature of this death correlates with certain experimental results (5). In a rat study where mesenteric arteriovenous occlusion was compared with separate mesenteric arterial and mesenteric venous occlusion, venous occlusion showed more rapid progression to full thickness necrosis (5). Ischemic damage extending to the muscularis occurred after to nine hours in the arteriovenous model and in the arterial model, but only four to seven hours in the venous occlusion model (5). In another bowel ischemia animal model, gram negative bacteria enter the circulation from the intestinal lumen within five hours (6). Gram negative bacteria possess an endotoxin (7). This is a cell wall component that produces shock and death when present in the bloodstream (7). In an animal model of severe hemorrhagic shock, gram negative bacteria enter the bloodstream in one to two hours (8). These experimental results suggest that the infarction in this patient occurred close to the time of death.

This patient suffered a sudden death while attending a baseball

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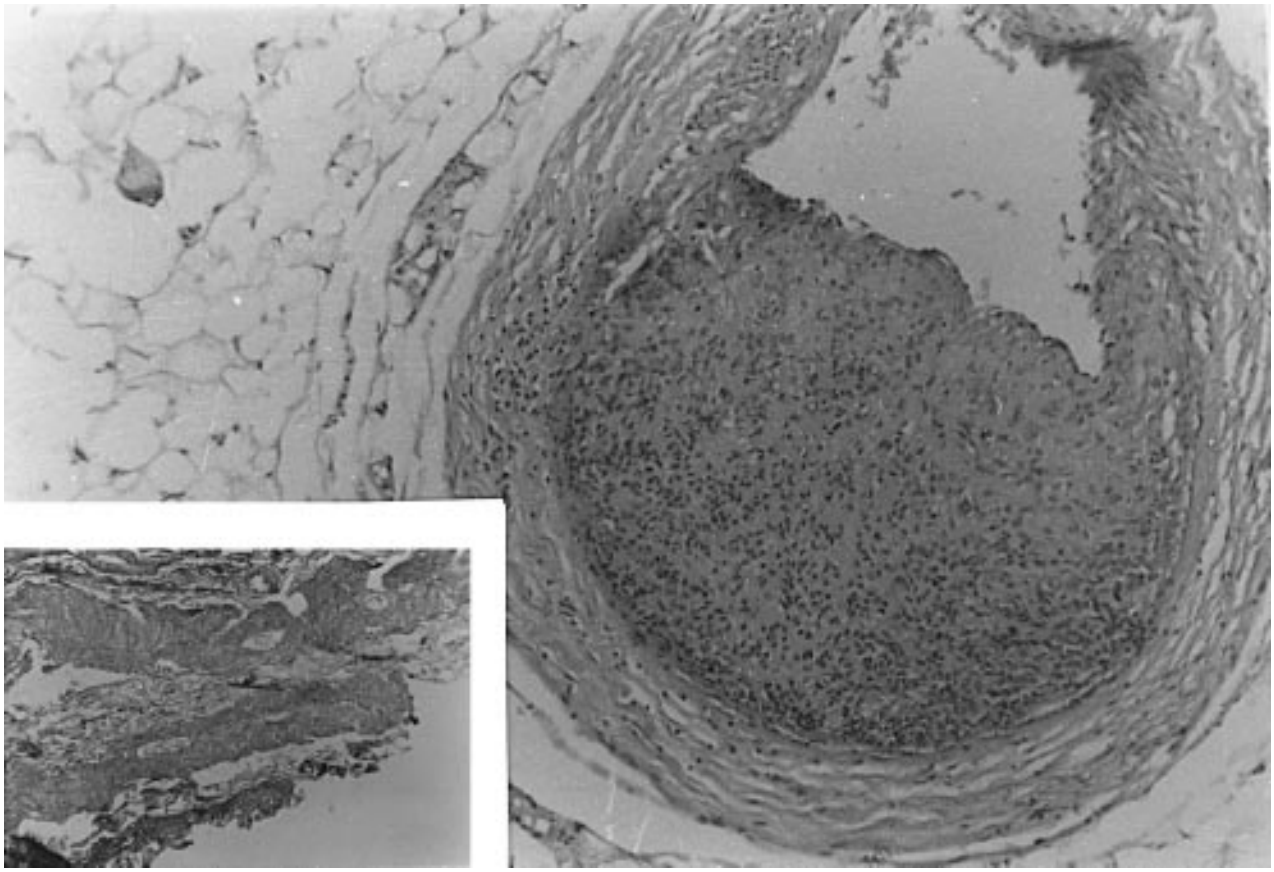

FIG. 1—*Venule showing partial luminal obstruction by hyperplastic myointima (H&E × 400). Inset: Infarcted jejunum showing separation of inner and outer layers of muscularis externa (H&E × 100).*

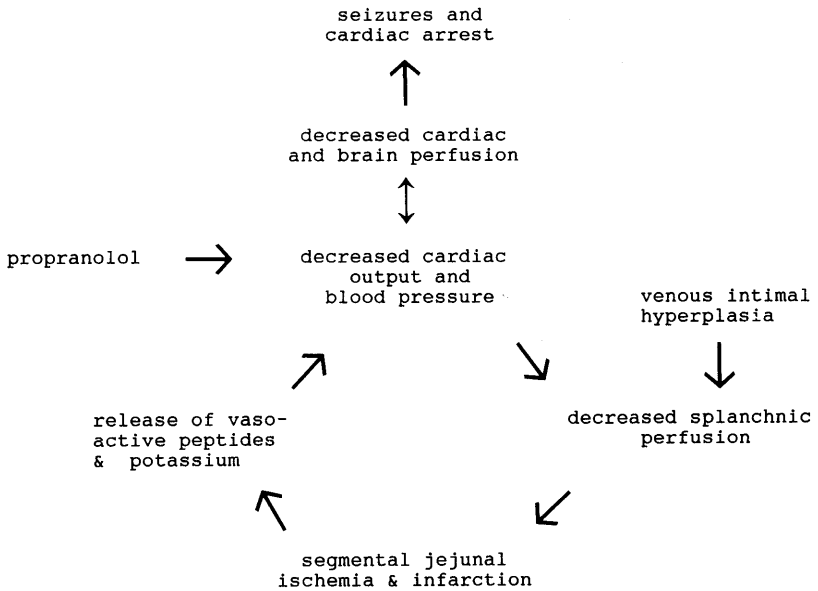

FIG. 2—*Mechanism I.*

game. Except for hypertension treated with propranolol and mild venous myointimal hyperplasia discovered at autopsy, she had no other medical conditions. To explain this death, two similar mechanisms are possible. In the first mechanism (Fig. 2), propranolol induces depressed cardiac output and hypotension. This leads to decreased splanchnic perfusion. This effect is enhanced by the venular disease in the mesenteric circulation. Decreased splanchnic perfusion leads to segmental jejunal ischemia and infarction. This causes release of potassium ions and bacterial endotoxin causing decreased cardiac output and hypotension in a positive feedback

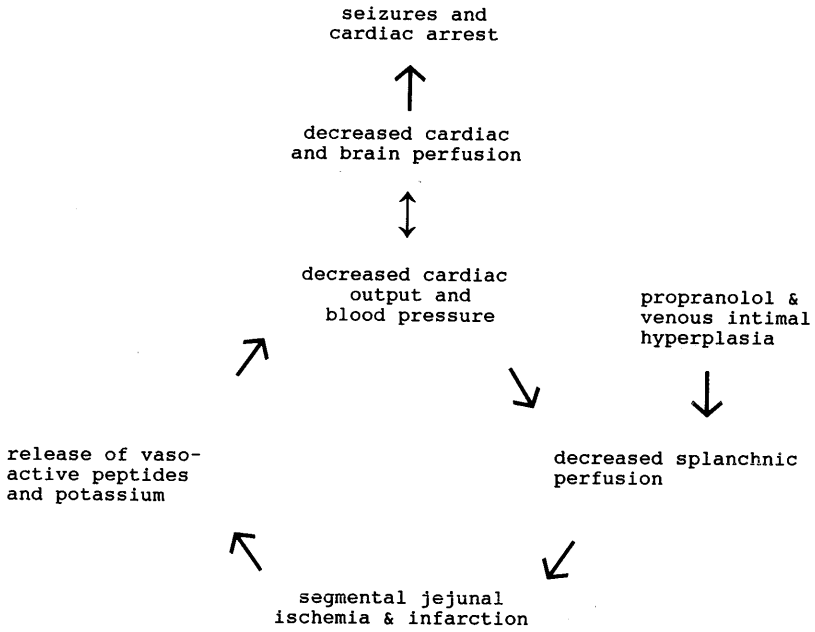

FIG. 3—*Mechanism II.*

loop (6,7). The depressed cardiac output and hypotension cause decreased heart and brain perfusion resulting in the terminal events of seizures, chest pain, cardiac arrest and death. In the second mechanism (Fig. 3), propranolol inhibits splanchnic circulation, leading to segmental jejunal ischemia and infarction (1–3). This causes release of vasoactive peptides and potassium ions, leading to depressed cardiac output and further depressed splanchnic perfusion in a positive feedback loop. Small vessel disease exacerbates the perfusion deficit in the mesenteric field (4). The depressed cardiac output and hypotension lead to depressed brain and cardiac perfusion, leading to the terminal events of seizures, chest pain, cardiac arrest and death.

In another interesting case of drug-induced intestinal ischemia, a vascular anomaly in the splanchnic circulation contributed to the production of intestinal ischemia (9). In contrast to the case presented here, the lesion in that case is a degeneration of the inner elastic membrane of the splanchnic arterioles. This elastic membrane degeneration may represent a direct effect of cocaine on the splanchnic arterioles. Since propranolol inhibits proliferation of smooth muscle cells, the mesenteric venular myointimal hyperplasia was not caused by propranolol (10).

Because it decreases mesenteric blood flow, propranolol is contraindicated in a patient with widespread symptomatic mesenteric venous myointimal hyperplasia. This case also demonstrates a contraindication for use of propranolol in mild asymptomatic forms of mesenteric venous myointimal hyperplasia. Thus, this case is a non-preventable unexpected sudden death due to a combination of propranolol induced compromise of the mesenteric blood flow and initially non-discoverable asymptomatic mild mesenteric venous myointimal hyperplasia.

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