IMAJ • VOL 13 • MARCH 2011

Extensive Epidermal Necrosis due to Terlipressin

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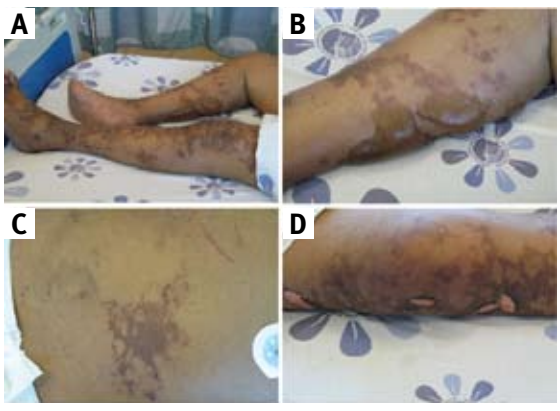
KEY WORDS: terlipressin, upper gastrointestinal bleeding, skin necrosis, cirrhosis

IMAJ 2011; 13: 180–181

Terlipressin (triglycyl-lysine vasopressin, Glypressin®, Ferring), an arginin-vasopressin analogue, is a potent vasoconstrictor with prolonged duration of action. Its effect on the splanchnic circulation results in prolonged reduction of portal venous pressure. For this reason it is routinely used in the management of bleeding esophageal varices and hepatorenal syndrome, well-known complications of portal hypertension in cirrhotic patients [1]. In the management of bleeding esophageal varices, terlipressin was shown to decrease mortality, reduce the failure rate of initial hemostasis and reduce the number of emergency procedures to stop uncontrolled bleeding or rebleeding [1]. Terlipressin was also shown to improve renal function and increase reversal rates of hepatorenal syndrome [1]. Although terlipressin has improved survival in cirrhotic patients, it may cause some well-known adverse effects. Those adverse effects are usually mild and include paleness, increased blood pressure, arrhythmia, headache, gastrointestinal manifestations and electrolyte imbalances [1]. This report discusses terlipressin-induced extensive skin necrosis, an unfamiliar adverse effect of this medication.

Terlipressin-induced epidermal necrosis. Epidermal skin necrosis in legs **[A and B]** and abdomen **[C]** following terlipressin treatment. During the following days, extensive areas of skin progressively detached **[D]**.



PATIENT DESCRIPTION

A 66 year old man with alcoholic cirrhosis was admitted due to ascites, encephalopathy and dyspnea. His medical history included obesity (body mass index > 30 kg/m^2), ischemic heart disease, benign prostate hypertrophy, diabetes mellitus type 2 with diabetic nephropathy, and mild chronic renal failure (creatinine 195 µmol/L). His cirrhosis score was CHILD C and was accompanied by portal hypertension-related manifestations, including refractory ascites and hypersplenism-related pancytopenia. Laboratory evaluation revealed pancytopenia, international normalized ratio 2.62, creatinine 230 µmol/L, blood urea nitrogen 20 mmol/L, and metabolic acidosis.

The ascites was controlled with large-volume paracentesis together with albumin and diuretic therapy. The fluid analysis showed transudate without evidence of infection. Twenty-four hours later the patient developed melena followed by hematemesis, which led to a decrease in hemoglobin from 100 to 70 g/L within several hours. To control the bleeding, the patient received multiple packed red cell transfusions as well as fresh frozen plasma and vitamin K in order to maintain target hemoglobin around 80 g/L. He was also treated with omeprazole, neomycin, lactulose and deralin, but the hemorrhage persisted. Endoscopy demonstrated multiple blood clots inside the stomach, making it technically difficult to evaluate the specific source of the bleeding. Given his general condition, the patient was not a candidate for surgical management.

Because the hemorrhage continued, terlipressin was started at a dose of 2 mg every 4 hours according to the manufacturer's instructions. Within 24 hours the hemorrhage gradually subsided and ceased completely after 48 hours. Terlipressin was reduced to 1 mg every 4 hours for an additional day. Repeated endoscopy did not demonstrate esophageal varices or another overt bleeding source.

Two days after terlipressin was discontinued, dark-greyish skin lesions began to emerge, especially on the thighs, calves and abdomen [Figures A and C]. On the following day, epidermolysis was clinically apparent and progressed to other parts of the body, including the arms but sparing the hands and feet. Wide areas of skin were covered with bullas filled with exudate [Figure B].

Cultures from the exudate as well as blood cultures were sterile, suggesting that infection was not the cause of this complication. During the next few days, extensive areas of skin progressively detached [Figure D]. Histological analysis of those specimens revealed desquamating epidermal tissue, which implied that the macroscopic bullas were the result of epidermal detachment. The blood supply to the damaged skin areas was assessed by Doppler ultrasound, which demonstrated normal arterial blood flow in the major arteries (radial, popliteal, tibialis poste-

rior, and dorsalis pedis). Finally, all the prescribed medications were revised to consider the possibility of drug-induced reaction.

Thorough investigation revealed that terlipressin was the latest medication to be introduced, and in the absence of other plausible explanations the skin lesions were attributed to terlipressin. In the meantime both liver and renal function deteriorated. A few days later the patient became profoundly comatose, acidotic and hypotensive, and died 14 days later due to cirrhotic complications.

COMMENT

Terlipressin has become extremely important in the management of bleeding esophageal varices and hepatorenal syndrome due to its relatively safe adverse effects profile as well as its prolonged half-life, which enables comfortable administration in intravenous boluses instead of by continuous drip – the customary method for most other vasoconstrictors [1]. While terlipressin is rather selective in its action on the splanchnic circulation, it also affects the systemic circulation, to a lesser extent, and in extremely rare cases has caused severe ischemia to the skin [1-3].

After thorough investigation ruled out infection and adverse effects of other prescribed medications in our patient, it was reasonable to assume that skin blistering following skin necrosis was a probable adverse effect of terlipressin treatment, especially since terlipressin was previously reported to cause ischemic manifestations in various tissues [3]. Under those circumstances, nitrate therapy might be beneficial in ameliorating the ischemic effect caused by terlipressin. However, our patient was hypotensive and nitrate therapy was therefore contraindicated.

This adverse effect is rare, yet its severity warrants that it receive special medical attention. To date, this extremely rare adverse effect was documented in only a handful of case reports [1-3]; those patients suffered from cirrhosis due to various etiologies for which terlipressin was prescribed to treat different indications. In all cases including ours, skin manifestations evolved after several days of treatment, implying a dose-related effect. However, this is the first report on skin manifestations evolving *after* the termination of terlipressin treatment. This phenomenon can be attributed to the long-acting vasoconstrictive effect of terlipressin. This important finding must alert the physician to act with caution when considering other medications with additive effect and stresses the importance of carefully monitoring the adverse effects of terlipressin even after its discontinuation.

Interestingly, in all the cases skin necrosis was documented in a particular distribution in different areas of the skin while sparing the fingers and toes, suggesting that this adverse effect is not a simple case of hypotension-induced ischemia. This is particularly relevant because monitoring systemic arterial blood flow is not useful for predicting the development of skin necrosis. This complication, however, can be related to the unique distribution of the target receptor of terlipressin – the vasopressin receptor type 1 (V1 receptor), which is located in smooth muscles of the blood vessels, mainly in the territory of the splanchnic circulation, kidney, myometrium, bladder, adipocytes, and skin circulation [4]. Thus, the damaged areas in our case reinforce the probability of terlipressin as the cause.

These findings enable us to predict that ischemic skin manifestations will probably emerge alongside the unique distribution of the V1 receptors, particularly in wide areas of skin such as the thighs and abdomen, but not in the hands and feet where the skin tissue is relatively small in diameter.

This report describes our successful experience with terlipressin in terminating upper gastrointestinal bleeding that was not related to esophageal varices. To date, terlipressin is mainly indicated for bleeding from esophageal varices. Although terlipressin is probably useful in the management of gastrointestinal bleeding from sources other than esophageal varices, its efficacy in such cases was hardly ever investigated, probably because massive bleeding in such cases is uncommon. The literature on this topic is still in its infancy, and in an attempt to perform a meta-analysis on the efficacy of terlipressin in the management of non-varices upper gastrointestinal bleeding, May and Musa [5] concluded that the data in the literature were insufficient to establish reliable guidelines for use of terlipressin in non-varices upper gastrointestinal bleeding.

Finally, with regard to other reports [1-3], the factors most associated with terlipressin-induced skin necrosis were obesity and hypovolemia. Obesity is particularly relevant since the maximal dose of terlipressin is administered according to weight. Thus, paradoxically, terlipressin is given in higher doses to patients with this predisposing risk factor; we therefore suggest that guidelines for dose adjustment be discussed and developed.

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