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SOFT TISSUE NECROSIS DUE TO NOREPIINEPHRINE INFUSIONS
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A number of cases have been reported in recent years of skin slough secondary to the intravenous administration of norepinephrine. This complication is not infrequent in patients receiving this drug. The mortality of those receiving more than minimal dosage is sufficiently high to prevent the complication from becoming apparent in many instances. The necrosis can be heroic in proportions and the morbidity several times that of the condition being treated.

The earlier reports in the literature were concerned with known extravasation at the infusion site. It was felt that careful insertion of a polyethylene catheter well into the vein would obviate the danger of necrosis.

It was soon apparent that insertion of the catheter atraumatically well into the vein was no protection against necrosis. Necrosis has been noted 20 centimeters proximal to the catheter tip. Impure drugs were considered also, but this was ruled out by several lots of the drugs behaving in a similar manner.

It is now apparent that ischemia in the superficial soft tissue of the extremity being used for the infusion is a risk inherent in the use of norepinephrine. Close has suggested the use of a catheter inserted through a high saphenous phlebostomy into the iliac vein as a method of avoiding necrosis. The immediate dilution of the infusion and adequate blood flow certainly should offer maximal protection against complications.

Several cases have been seen by plastic surgery service in consultation and are recounted briefly below.

CASE #1 — A.B. — A 52 year old white female admitted with pyelonephritis and lithiasis in her only kidney. She was anuric. NPN was 148 mg%; B.P. 80/60. Norepinephrine 8 meg/per cc. was started through a polyethylene catheter inserted in an ankle cutdown, and continued for 24 hours. Therapeutic response was good. No gross extravasation was noted. At the end of 48 hours reddened areas were noted in the anterior tibial areas at level of the catheter tip. Over the next four days these areas slowly demarcated. The necrotic areas were debrided and split thickness skin grafts applied 26 days after admission. The take of the grafts was moderately good. Several small unhealed areas remained which healed within the month after discharge.

CASE #2 — T.S. — A 51 year old white male with advanced multiple sclerosis admitted unconscious and areflexic to the Emergency Room. Norepinephrine 8 meg. per cc. was administered intravenously through an ankle cutdown, and continued for 36 hours. At this time edema and pallor were noted above the cutdown. This was followed by redness and bleb formation progressing to a purplish hue over the next 48 hours. The wounds were debrided under general anesthesia, 18 days after admission and split thickness skin grafts applied. The grafts healed well except over a small area of exposed tibia. The exposed bone was removed and the area healed without further therapy.

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Tissue Necrosis due to Norepinephrine

Figure I, Case I
Tissue injury and necrosis from intravenous norepinephrine.

Figure II, Case II
Necrosis, left, and repair by skin graft, right.
CASE #3 — D. J. — A 60 year old colored male admitted with asthmatic bronchitis. On the day following admission he developed an acute vasomotor collapse, presumably from iodide sensitivity. Blood pressure was 60/0. Norepinephrine 4 mcg. per cc. was started in an arm vein and a satisfactory response obtained. The patient removed the IV needle at the end of 24 hours and his pressure promptly fell to 68/0. The norepinephrine infusion was started in the opposite arm and continued for an additional 24 hours. Superficial blistering developed in 24 hours and slowly progressed to dry gangrene of both antecubital areas. One month after admission the sloughs were excised under local anesthesia and split thickness skin grafts applied. The healing of the grafts was poor. Necrotic areas were debrided and healing obtained by application of stored autogenous skin grafts.

CASE #4 — H. M. — A 64 year old white female admitted with cholecystitis and lithiasis, critically ill. Her condition steadily worsened with onset of congestive failure and unconsciousness. Started on Norepinephrine which was given 8 meg/cc over a 12 hours period. Difficulty was experienced with extravasation and the cutdown had to be restarted. Necrosis was noted first as an annular blistering with an apparently viable center portion about 4 x 6 cm. Because of her precarious general condition due to recurrent bouts of pancreatitis, it was felt surgical treatment of the necrotic area should be deferred. Debridement was carried out on the ward piecemeal and the patient discharged with an unhealed lower leg ulcer. After one year the ulcer had not healed. The patient was then re-admitted and the ulcer closed by split thickness skin grafts.
CASE #5 — M.P. — A 34 year old colored female seen in the Emergency Room with a lacerated extensor tendon of the hand. After careful questioning she was given an intramuscular dose of penicillin. She collapsed within a few minutes. Blood pressure was 40/0. Intravenous Benadryl and Cortisone were administered with a satisfactory immediate response. Norepinephrine 4 meg. per cc. was given by infusion into the antecubital vein. Eight hours later the infusion was found to have infiltrated into the tissues. The arm and forearm were edematous and markedly cold. It was felt that this patient would surely develop necrosis. 50 cc. of xylocaine 1% and 1500 units of Hyaluronidase were infiltrated into the area of extravasation. The swelling and ischemia were alleviated and progress from this point was uneventful.

Treatment

The treatment of the manifest necrotic area is not materially different from sloughs secondary to a number of other therapeutic or physical agents. Debridement of the necrotic skin is accomplished under suitable anesthetic. The precarious general state of some of these patients necessitates the use of local anesthesia. The fat necrosis often extends beneath viable skin, especially along the course of blood vessels. It may be necessary to delay the application of skin grafts for several days if there is any doubt as to the adequacy of the debridement.

It is naturally desirable to initiate treatment which will prevent the onset of necrosis. The treatment of choice if extravasation is noted is the infiltration of regitine 5 to 10 mg. in 15 cc. of diluent into the extravasated area. There may be reluctance...
on the part of physician treating the patient to risk giving a therapeutic antagonist which may cause a return of the hypotension he has been vigorously combating. We would suggest that if the extravasation is recognized early that xylocaine and hyaluronidase be infiltrated into the involved area and if improvement is noted, further treatment can be withheld. The use of hyaluronidase alone has been shown to be ineffective except to reduce the swelling. In the patient who is well stabilized, however, regitine is preferable to other agents. Warm applications to relieve the vasospasm carry a high risk of enhancing the amount of necrosis by increasing the metabolic demands of the ischemic tissue. histamine and mecholyl iontophoresis have been recommended but seem to be unduly involved. Allowing spontaneous separation of the slough and healing to take place may take months as illustrated by Case #4. During this prolonged period of healing, a portal is open to potentially dangerous infection.

Discussion

The use of Norepinephrine as a life saving measure in hypotension in spite of its propensity to cause soft tissue necrosis can be stoutly defended. Its prolonged usage to the exclusion of proper blood volume or electrolyte replacement or correction of cardio respiratory imbalances, and its use for less emergent hypotensive states, may place the physician in an untenable position if tissue necrosis ensues.

Conclusions

Norepinephrine causes profound ischemia of the tissues surrounding the vessel into which it is introduced. This is due to extravasation of the Norepinephrine into the surrounding tissues. It is not dependent on gross leakage from the vessel at the infusion site. This extravasation is apparently enhanced by increased capillary permeability associated with hypotensive states.

It is incumbent upon the physician to observe the infusion sites and areas between the infusion and major venous channels at frequent intervals during therapy. Ischemia can be noted early and treatment can be instituted if feasible or notations made in the record why treatment is being deferred.

BIBLIOGRAPHY