Accidental intra-arterial injection

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SUMMARY Accidental intra-arterial injection of intramuscular antibiotic preparations is described in 3 cases in infants. In 2 benzathine penicillin was injected, and in 1 rolitetracycline. The clinical features are dominated by arteriolar obstruction which produces gangrene of the most severely affected limb. In addition, neurological involvement occurs when vessels to nerves or spinal cord are involved. The anterolateral aspect of the thigh is preferable to the buttock as a site for intramuscular injection, and a short (2.5 cm) needle should be used to minimise the risk of intra-arterial injection.

The effect of accidental injections of bismuth into the superior gluteal artery was described by Gammel (1927) who found reports of 30 such cases consequent on injections of mercury or bismuth into the buttock. One mechanism had been demonstrated by Freudenthal (1924) who found bismuth crystals blocking the cutaneous arteries at necropsy. Nicolau in 1925 produced an analogous clinical picture by injecting into the ear arteries of rabbits.

More recently a similar clinical picture has been described after intramuscular injection of an antibiotic, penicillin (Shaw, 1966; Knowles, 1966; Brown and Nelson, 1966; Gordon and Dove, 1972). We report here 3 such cases, in 2 of which arteriography was performed.

Case reports

Case 1. A 2-month-old coloured girl, weighing 2940 g, was admitted with a past history of prematurity, gastroenteritis, indirect hyperbilirubinaemia, and hypoglycaemia. Benzathine penicillin 1 ml and iron dextran (Imferon) 1 ml had been given into separate buttocks for a chest infection. One hour later discoloration of the limbs and distress were noted by the mother who brought the child back to hospital.

On admission the infant was restless. Diffuse reticular mottling extended up to the umbilicus (Fig. 1). There was marked capillary stasis in the legs. By the next day when a surgical opinion was sought, areas of capillary staining were present on the feet and buttocks. Both dorsalis pedis pulses were palpable. There was loss of sensation in the right foot with paralysis of ankle movements.

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Arteriography showed that the right superior gluteal artery did not fill (Fig. 2). There was stasis of the contrast medium distal to the popliteal artery bifurcation on the right side, with no distal filling

Fig. 1 Case 1, showing mottled reticular appearance of both legs.

Fig. 2 *Case 1. Arteriogram after retrograde injection of contrast medium via right femoral artery (a) During injection, showing nonfilling of right superior gluteal artery; (b) 4 seconds after injection, contrast reaching popliteal junction on the right and foot vessels on the left; (c) 16 seconds after injection showing persistence of contrast in the popliteal vessels.*

in spite of the palpable pulses. On the left side there was prolonged visualisation of contrast in the small vessels of the foot.

Tissue destruction was indicated by enzyme studies which showed SGOT 270 units, SGPT 140 units, creatine phosphokinase 1200 units, LDH 1075 units. Other investigations included Hb 9.5 g/dl, reticulocytes 10.7%, white cell count $22.3 \times 10^9/l$. Prothrombin index was 87.5% and the serum fibrinogen 1.88 g/l. Blood urea was 55 mg/100 ml (9.13 mmol/l).

Treatment was with heparin, low molecular weight dextran, and prednisone. There was steady clinical improvement with recovery of sensation and movement. Gangrene of the distal foot developed, followed by spontaneous amputation. Further full thickness loss occurred in the buttock following the distribution of the gluteal artery (Fig. 3). Trimming of bone and skin grafting resulted in a functional forefoot. Healing in the buttock and leg left unsightly scars. She remained well, and is walking normally 3 years later after further trimming of bone ends.

Case 2. A 4-month-old black girl, weighing 5200 g, was given an intramuscular injection of 1.5 ml benzathine penicillin. 2 days later the mother noticed

Fig. 3 Case 1, showing necrotic areas in the buttock and calf. (The gangrene of toes and forefoot is not shown.)

discoloration and weakness of the left leg. Examination showed a healthy looking infant. There was paralysis of both legs, anus, and bladder. Sensory loss extended to the upper thighs. Both legs were cold with some mottling in the left leg where areas of capillary staining were noted. There was early gangrene of the toes and pulses could not be felt below the femoral artery. An indurated linear, slightly discolored nonblanching area in the superior gluteal distribution of the left buttock indicated the site of injection. On the right, pulses were present but there was some capillary stasis in the foot.

Arteriography showed features similar to Case 1 but the gluteal vessels were patent. There was marked stasis on both sides with failure of distal filling on the left. Contrast persisted in the upper tibial vessels for 30 seconds.

Treatment included antibiotics, heparin, and low molecular weight dextran. Autoamputation through

the ankle joint preceded conservative trimming, suturing, and skin grafting. There was a slight improvement in the neurological deficit. The baby died at home 2 weeks after discharge apparently from an acute chest infection.

Case 3. A 6-week-old coloured boy, weighing 2570 g, had received daily intramuscular injections of rolitetracycline 175 mg in a country hospital. He had been admitted with diarrhoea, vomiting, and fever 3 days before transfer to our hospital. The right leg was noted to be swollen the day before transfer.

On admission the infant was pale and listless with tachycardia. The right leg was paralysed. Frank distal gangrene extended to midcalf and bluish discoloration and ecchymosis to the thigh which was swollen. There were less severe changes in the left leg. Patchy mottling similar to Case 1 was noted on the back above the iliac crests. Only the left femoral artery could be palpated. Plasma sodium 145 mEq/l; potassium 4.6 mEq/l; chloride 118 mEq/l; urea 180 mg/100 ml (29.9 mmol/l); total bilirubin 0.5 mg/100 ml (8.55 μ mol/l); SGOT 42 units; there was a mild metabolic acidosis. Urine showed a trace of albumin and an occasional granular cast. Hb 4.6 g/dl; white blood count 1.8×10^9 /l; platelets 28×10^9 /l; fibrinogen 0.54 g/l; fibrinogen degradation products in the blood were $>10 \mu$ g/ml.

There was some deterioration over the first few hours, particularly in the left foot. This responded dramatically to heparin, low molecular weight dextran, and blood transfusion. The haematological abnormalities returned to normal over a few days. After autoamputation through the ankle joint projecting bone ends were trimmed, the tissues approximated, and areas of skin loss grafted. The child was walking well with a prosthesis 2 years later.

Discussion

Accidental intra-arterial injection of penicillin is most common in small babies (Table). It seems likely that the relatively large doses injected into the small arterial tree are responsible for the more florid presentation. In Gammel's (1927) 3 adult cases following injections of bismuth, the ischaemic area was localised to the buttock and in one the sciatic nerve was involved. In Gordon and Dove's (1972) 16-year-old boy, a massive 8 ml of penicillin aluminium monostearate was used.

The underlying mechanism was first suggested by Freudenthal in 1924. The viscous penicillin solutions are difficult to inject through the needle and must therefore be given forcefully (Gordon and Dove, 1972). Aspiration is no guarantee that the needle tip

Table Main features of reported cases

Author	Age (m)	Agent	Volume (ml)	Time of onset	Pulses	Gangrene	Rectum or bladder involvement	Sciatic palsy	Paraplegia	Enzymes raised
Knowles (1966)	2	Benzathine penicillin & procaine penicillin	2	Immediate	Present	Yes	Yes	Yes	No	—
Shaw (1966)										
Case 1	15	as above	2	Immediate	—	No	No	No	Yes	—
Case 2	2½	as above	2	Immediate	Present	No	„	Yes	No	—
Brown & Nelson (1966)										
Case 1	8½	Benzathine penicillin G	2	1 d	Absent	Yes	„	„	No	—
Case 2	7½	Penicillin		½ h	Present	„	Yes	„	Yes	—
Gordon & Dove (1972)										
	16 y	Penicillin aluminium monostearate	8	Immediate	—	„	Yes	„	No	Yes
Loubser (1973)	2½	Benzathine penicillin G	2	Immediate	—	„	No	No	Yes	—
Present study										
Case 1	2	as above	1	1 h	Present	„	„	Yes	No	Yes
Case 2	4	as above	1.5	2 d	Absent	„	„	No	Yes	—
Case 3	1½	Rolitetraacycline	1	Hours	Absent	„	„	No	No	—

is not in the artery (Knowles, 1966). During administration, particularly in a recalcitrant child, the needle may move and come to lie in the artery. When the drug is injected forcefully retrograde flow up into the iliac vessels occurs. In a small child it may shoot up into the aorta and be distributed to the spinal arteries, internal iliac vessels, and down both legs.

The characteristic diffuse mottling may extend up to the level of the umbilicus. This is followed by ischaemia progressing to frank necrosis. Distal pulses may be present in spite of the evident sluggish flow of blood. Gangrene may involve one or both legs but is more severe on the side of the injection. The distal foot is usually affected and there may be necrotic areas higher on the leg. Gangrene of the buttock, the perineum, the vulva, the scrotum, and the penis may follow embolisation down the internal iliac arteries. Characteristically, areas of maximum involvement with gangrene occur on the buttock in the distribution of the gluteal arteries.

Embolisation of the middle and inferior rectal arteries may result in a granular proctitis and rectal bleeding (Knowles, 1966; Gordon and Dove, 1972). The bladder may be affected (Brown and Nelson, 1966). The artery to the sciatic nerve arises from the inferior gluteal artery and sciatic nerve palsy can occur (Knowles, 1966). If the spinal artery given off by the lumbar branch of the iliolumbar artery is embolised, the result is a transverse myelitis; paralysis of both legs, bowel, and bladder will develop (Shaw, 1966). Serum enzymes may be raised due to necrosis of affected muscles (Gordon and Dove, 1972).

Sciatic and radial nerve palsies have all too often

been attributed to the incorrect injection directly into the nerve, whereas many palsies have more probably been due to inadvertent intra-arterial injection. Blame has consequently often been unfairly placed on the physician or nurse administering the injection (Knowles, 1966).

Case 3 had disseminated intravascular coagulation (DIC) which might be attributed to a preceding viral or bacterial infection. We believe that the tetracycline triggered the DIC process as a result of its direct irritant action on the vascular endothelium.

Loubser (1973), using apes and baboons, was able to produce similar clinical features by injecting benzathine penicillin into the superior gluteal artery and demonstrated slowing of arterial flow. In addition, he injected barium sulphate into the gluteal arteries of baboons and demonstrated the distribution of barium through the arterial system by radiography. Arteriography in our 2 cases showed very marked stasis in the arterial tree. The contrast failed to reach the foot on the most severely affected side, although in Case 1 the dorsalis pedis was palpable.

The actual mechanism whereby arteriolar occlusion is produced requires elucidation. Freudenthal (1924) showed bismuth crystals in the gangrenous tissues suggesting a mechanical obstruction. The antibiotic preparations responsible are viscous suspensions of antibiotics of low solubility designed for slow absorption (benzathine penicillin, penicillin aluminium monostearate, rolitetraacycline). These finely suspended particles might be capable of obstructing finer vessels. Ehringer *et al.* (1971), however, report 2 cases of gangrene where penicillin intended for intravenous use was accidentally given

intra-arterially. We have seen one case of localised gangrene where sodium penicillin G was injected into an 'intravenous' infusion inadvertently inserted into the dorsalis pedis artery. These cases led us to the conclusion that there is a direct chemical effect on the arterioles.

Apart from the risk of direct injection into the sciatic nerve the possibility of intra-arterial injection with its unfortunate sequelae must render the buttock an unsuitable site for injection, especially in small babies. The anterolateral thigh is the alternative and preferable site, using a needle no longer than 1 inch (2.5 cm), as recommended by Talbert *et al.* (1967). They report a case of femoral artery thrombosis in a child due to periarterial injection of penicillin. Injection into the lumen of the artery is clearly possible.

We have used full heparinisation together with daily low molecular weight dextran in our cases. In Case 3 with DIC the response was immediate. Vasodilators or sympathectomy have not been used. Conservative amputations preserving as much tissue as possible have given good functional results.

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