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Fatal complications of intramuscular and intra-articular injections

Marja-Leena Kortelainen and Terttu Särkioja

Department of Forensic Medicine, University of Oulu, Kajaanintie 52 D, SF-90220 Oulu, Finland

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Summary. Four fatalities related to intramuscular and intra-articular injections are reported. In two of these cases a *Staphylococcus aureus* sepsis developed, as a consequence of injections into the left hip joint in one and in the lateral upper quadrant of the gluteal region in the other. The intra-articular injection of triamcinolone produced severe pain, but no marked signs of purulent arthritis were seen at autopsy, probably because of the anti-inflammatory effect of the corticosteroid. A cutaneous infection was seen in the gluteal region of the other patient, but no apparent abscess formation. In another case of intra-articular injection, purulent knee joint arthritis developed after an injection of glucosaminoglycan. The patient died of renal insufficiency, which was probably connected with the treatment of the arthritis with tobramycin and cefuroxim. The fourth case was that of a mentally ill patient who suffered sudden cardiac arrest after an intramuscular injection of chlorpromazine, but with no apparent signs of an anaphylactic reaction. It is suggested that vasodilatation and drop in blood pressure caused by the chlorpromazine could have had some effect, while cardiotoxicity of other psychotropic drugs with which he had been treated cannot be ruled out.

Key words: Intramuscular, intra-articular injection, fatalities – *Staphylococcus aureus* sepsis – Corticosteroids

Zusammenfassung. Es wird über vier Fälle berichtet, in denen intramuskuläre und intra-artikuläre Injektionen Komplikationen mit tödlichem Ausgang zur Folge hatten. In zwei von diesen Fällen erwies sich eine intramuskuläre bzw. intra-artikuläre Injektion als Ausgangspunkt einer Staphylokokkensepsis. Auf die intra-artikuläre Injektion ins Hüftgelenk folgten große Schmerzen, die Autopsie zeigte aber keine augenfälligen Anzeichen einer pyogenen Arthritis. Dieses Phänomen steht wahrscheinlich in Zusammenhang mit der anti-inflammatorischen Wirkung der Kortikosteroide. Im anderen Fall be-

Offprint requests to: M.-L. Kortelainen

stand eine lokale Hautinfektion (kein glutealer Abszess!). Trotzdem wurde *Staphylococcus aureus* im Blut nachgewiesen und andere lokale Infektionen konnten nicht diagnostiziert werden. Weiterhin wird eine Komplikation nach intra-artikulärer Injektion eines Glykosaminoglykanpräparats beschrieben, die eine schwere Infektion eines Kniegelenks verursachte. Dieser Patient starb an einer Niereninsuffizienz, die wahrscheinlich in Verbindung mit einer Antibiotikabehandlung mit Tobramycin und Cefuroxim stand. In diesem Material wird außerdem der Fall eines psychotischen Patienten beschrieben, der nach intramuskulärer Chlorpromazininjektion einen plötzlichen Herzstillstand erlitt, bei dem aber keine deutlichen Anzeichen einer anaphylaktischen Reaktion auftraten. Es wird vermutet, daß Vasodilatation und Blutdrucksenkung, verursacht durch Chlorpromazin, dem Tod des Patienten verursacht haben könnten. Die Kardiotoxizität anderer Psychopharmaka, mit denen der Mann behandelt war, kann auch nicht ausgeschlossen werden.

Schlüsselwörter: Intramuskuläre, intraartikuläre Injektion, Komplikation – Staphylokokkensepsis – Kortikosteroide

Introduction

Intramuscular and intra-articular injections entail a risk of both local and generalized complications that may even lead to charges being brought against medical personnel. Local adverse effects of intramuscular injections include abscess formation, nerve injuries and aseptic necrosis due to intra-arterial injection; these are referred to collectively as the Nicolau syndrome [7]. Purulent arthritis is a known complication of intra-articular injections. Severe complications of intramuscular injections include gas gangrene produced by *Clostridium perfringens* [8], staphylococcal sepsis [9] and toxic shock syndrome [1]. A more unusual severe infectious complication with group A beta-haemolytic *Streptococcus* has also been reported [5]. The possibility of a severe anaphylactic reaction is always present when a drug is administered parenterally.

To investigate the prevalence of fatal complications of parenteral injections and the medicolegal aspects associated with determining the basic cause of death and the manner of death in such fatalities, material was collected from the files of the Department of Forensic Medicine, University of Oulu and the autopsy protocols, histological samples, police records and case histories were reanalyzed.

Material

All cases in which a parenteral injection was stated as the basic cause of death or a contributing factor were collected from the files of the Department of Forensic Medicine, University of Oulu for 1986–1987. Of 1312 autopsies performed during this period from a total population of the area served by the University Central Hospital of 427000, 4 fatal complications of parenteral drug injections were found, which are described here.

Case 1. A 48-year-old, previously healthy male was admitted to hospital because of severe pain in the lumbar region. The diagnosis was acute lumbago with no

Fig. 1. Case 1: the injection channel in the gluteal region. The channel and the surrounding skin and subcutaneous tissue are infiltrated by numerous granulocytes, indicating suppurative infection at the injection site. HE, × 42.5

symptoms of sciatica. The patient was not receiving any regular medication and did not have any symptoms of other diseases. The severe pain was treated with several intramuscular injections of diclofenacum (Voltaren, Ciba-Geigy) and oral dextropropoxifen (Abalgin, Alfred Benzon). The patient returned home after 3 days but was readmitted to hospital 2 days later, still complaining of very severe pain in the lumbar region. He was again treated with intramuscular injections of diclofenacum to the upper quadrant of the right gluteal region. A septic fever developed and the patient went into a state of shock. A reddish oedematous area was seen around the injection site. Small pustules were seen in the lower extremities, but no other infectious foci were found. Gram-positive *Staphylococcus* was twice cultured from the blood and *Staphylococcus aureus* sepsis was diagnosed. Treatment began with a combination of two antibiotics, cefotaxim (Claforan, Hoechst) and netilmicin (Netilyn, Essex) and continued with cloxacillin (Ekvacillin, Astra Läkemedel) after the bacteriological diagnosis. Conventional treatment for septic shock was provided in a critical care unit, but the patient died 8 days after the first intramuscular injections and 3 days after the onset of septic symptoms.

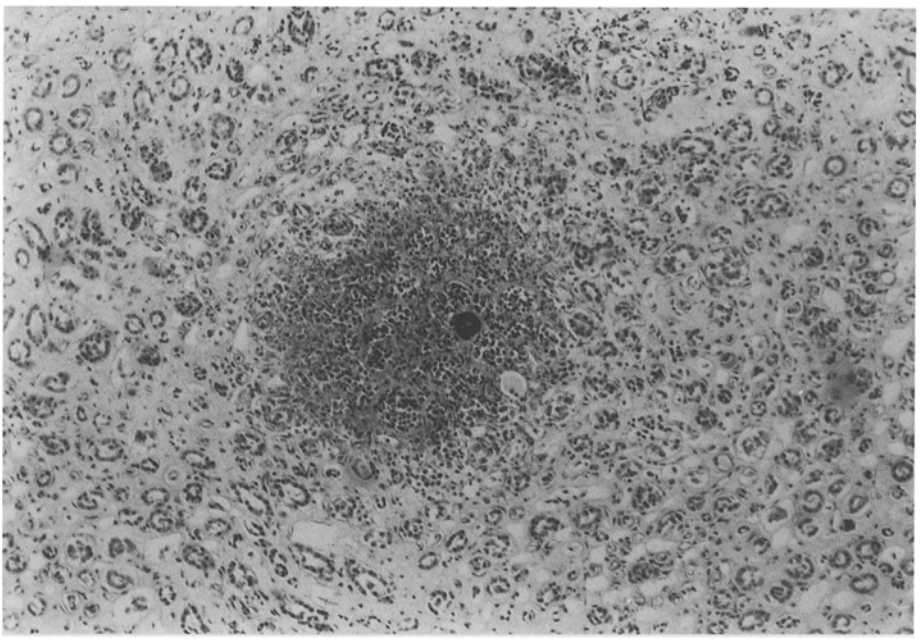

Fig. 2. Case 3: a septic embolus in the medullary region of the kidney. The arteriole is filled with bacteria and the perivascular tissue is infiltrated by granulocytes. HE, × 67

The autopsy findings were typical of septic shock. Small clusters of bacteria were seen in the myocardium and kidneys, and general shock-related degenerative changes were seen in other parts of the body. Pneumonia was also present. A reddish, oedematous area 12 cm in diameter was seen on the upper lateral quadrant of the right gluteal region, and microscopical examination revealed hyperaemia and granulocytes in the skin (Fig. 1). No other infectious foci were seen at autopsy. The cutaneous infection was stated as the basic cause of death and gram-positive sepsis as the immediate cause of death. The intramuscular injections were considered a contributing factor. The manner of death was left open, as the causality between the intramuscular injections and the infection remained speculative.

Case 2. A 35-year-old man with psychiatric anamnesis was brought to a local hospital because of mental confusion, aggressive behaviour and suicidal intentions. He was not known to have any somatic health problems, and the only medication he was taking was perphenazine (Peratsin, Lääkefarmos). He was given 50 mg chlorpromazine (Largactil, Medica) intramuscularly and cardiac arrest with asystole was recorded shortly afterwards. Resuscitation was followed by irreversible ischaemic brain damage and the patient died 1 week after the injection. Blood and urine samples were analyzed for routine toxicology, but no drug overdose or other intoxication was found, nor were there any clinical signs of somatic diseases that could have led to cardiac arrest. General anoxic brain damage and severe bronchitis with hyperplasia of the peribronchial and mediastinal lymph nodes were observed at autopsy and histologically. There were slight

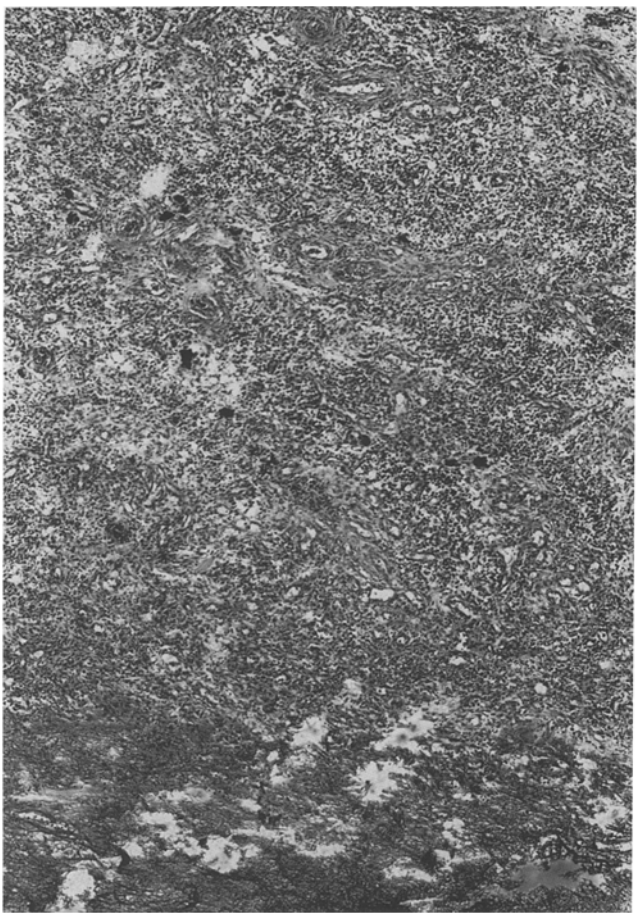

Fig. 3. Case 4: a suppurative infection in the synovial membrane of the knee joint with increased neutrophilic infiltration, oedema and vascular congestion. HE, × 42,5

atheromas in the arterial intimae but no chronic illnesses or other marked organ changes were seen.

The myocardium, liver and kidneys were morphologically normal except for non-specific changes caused by shock (myocardosis, hepatosis, nephrosis). The intramuscular injection of chlorpromazine was implicated as the basic cause of death leading to an irreversible ischaemic brain lesion. The terminal respiratory infection (bronchitis) was considered to be the immediate cause of death. Mental disorder was stated as a contributory factor, and the manner of death was regarded as a complication of medical care.

Case 3. A 78-year-old woman with a history of left hip joint arthrosis was given an intra-articular corticosteroid injection of triamcinolone (Lederspan, Lederle) to relieve the pain. Two days later increased pain in the left hip joint region was reported and a fever developed. The patient became somnolent during the following 3 days and *Staphylococcus aureus* was found in the blood culture. Some pneumonic infiltrate was seen on the X-ray plates. The patient died on the 6th day after the intra-articular corticosteroid injection. The autopsy findings were

characteristic of septicaemia: petechial haemorrhages in the ocular conjunctivae, respiratory tract, lungs, pericardium, endocardium and ventricular mucosa, and changes typical of shock in the myocardium, kidneys, liver and adrenals. Microscopical examination showed small clusters of bacteria and granulocytes in the lungs and kidneys (Fig. 2). There were fibrin thrombi in the arterioles and large numbers of perivascular leucocytes, indicating disseminated intravascular coagulation (DIC). Arthrosis of the left hip joint was diagnosed at autopsy. A large cutaneous haematoma measuring 2×12 cm covered the hip region, and minor bleeding was seen in the articular capsule, but no signs of purulent arthritis nor of any other infection were observed either macroscopically or microscopically. The surrounding tissues were also intact except for minor haematomas in the muscles around the joint. The intra-articular injection of triamcinolone was noted as the basic cause of death, as it had been followed by staphylococcal sepsis. The hip joint arthrosis was considered to be a contributory factor, and the manner of death was again stated as a complication of medical care.

Case 4. A 90-year-old man had received an intra-articular injection of glucosaminoglycan (Arteparon, Luitpold) in his left knee joint for severe arthrosis; he had been treated with the same agent 1–2 times a month for several years. Regular medication included digitalis and diuretics for coronary heart disease with myocardial insufficiency. On the patient's arrival at hospital his left knee was swollen, inflamed and tender. The synovial fluid was cloudy, the leucocyte count 65×10^9/l, 95% being granulocytes. The blood leucocyte count increased to 54.1×10^9/l, erythrocyte sedimentation rate (ESR) was 88 mm/h, and S-CRP was 200. *Staphylococcus aureus* was present in the synovial fluid in large numbers, and there was also some growth of *Streptococcus β-haemolyticus.* The patient was treated with cefuroxim (Zinacef, Glaxo) and tobramycin (Nebcina, Lilly) intravenously for 9 days and then cloxacillin (Staflocil, Orion) was substituted. Hyperkalaemia (serum potassium 6.9–8.6 mmol/l) and renal insufficiency (s-creat 869 mmol/l) developed, and the patient died on the 14th day after the intra-articular injection. Purulent synovitis was found in the left knee joint at autopsy (Fig. 3).

General shock-related changes were seen in the brain, myocardium, liver and spleen, with stress ulcerations in the ventricular mucosa. Necrosis of the renal proximal tubular epithelial cells, interstitial oedema and cellular casts in the distal collecting tubes were also seen. The intra-articular injection of Arteparon (glycosaminoglycan) was considered to be the basic cause of death. The concomitant purulent arthritis had been treated with two broad-spectrum antibiotics with known renal toxic effects, and renal tubular necrosis was considered to be the immediate cause of death in this case. The manner of death was similarly stated to be a complication of medical care.

Discussion

The fatalities described here represent four different types of complication connected with routine intramuscular and intra-articular injections. In the first case gram-positive bacteria spread from the infection in the right gluteal region. This was probably connected with the multiple intramuscular injections of an analgesic. The patient had some pustules on the lower extremities, but no gluteal pustules were either reported clinically or found at autopsy. It is possible, however,

that some minor cutaneous infection might have remained unobserved at the time of the intramuscular drug administration. It is of importance that no apparent abscess formation was seen in this case, but merely a diffuse cutaneous infection. This differs from the previous case reported by Zuber and Mall [9], who described two patients with staphylococcal sepsis originating from post-injection gluteal abscesses.

There are some reports of severe infectious complications of intramuscular corticosteroid injections [7, 9], and this study includes two cases in which elderly patients had received drugs by intra-articular injection, one into the hip joint and the other into the knee joint. The 78-year-old woman with hip joint arthrosis had no other infectious foci that could have been responsible for the severe generalized staphylococcal infection, nor was any pyogenic arthritis diagnosed at autopsy. We presume, therefore, that the corticosteroid itself (triamcinolone) may have weakened the local reaction in the joint and that some spreading of an infectious agent occurred in spite of the virtual lack of local signs.

The 90-year-old man (case 4), on the other hand, showed clear signs of pyogenic arthritis. No severe generalized infection was reported clinically, and the terminal uraemia was probably connected with the nephrotoxicity of the antibiotics used to treat the infection [3, 6].

The possibility of microbial contamination of the pharmacological agent itself did not arise in any of these cases, although such complications involving streptococci have also been reported [4]. There are a numer of reports of incidents in which unopened intravenous fluids have been found to be contaminated with micro-organisms, resulting in fatalities [2]. This intrinsic or iatrogenic microbial contamination is very rare, however [2], and the three infectious cases reported here more probably arose via an extrinsic route, e.g. from the patient's own skin or from the hands of the person giving the injection.

In the fourth case, an intramuscular chlorpromazine injection was followed very rapidly by cardiac arrest, but no typical anaphylactic reaction could be verified either clinically or at autopsy. One might speculate that the potent vasodilatory effect of the chlorpromazine and the consequent drop in blood pressure could have something to do with the circulatory failure. On the other hand, certain psychotropic drugs apparently have cardiotoxic effects [3], and long-term treatment can entail certain risks in this respect. This patient had been treated with another phenothiazide namely perphenazine. The cardiovascular response was extremely strong in this patient, however, and was therefore probably to some extent of an anaphylactic nature.

In conclusion, fatal complications seem to be extremely rare compared with the abundance of intramuscular and intra-articular injections of various drugs given in clinical practice. The medicolegal investigation of these cases can be problematical, however, because of the relative scarcity or even total absence of signs of infection or other processes leading to death. The causality between the known events can also be difficult to explain, and therefore the basic cause of death and the manner of death require careful consideration, particularly since these cases often raise questions regarding the proper course of medical care.

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