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Nadroparin-induced calcinosis cutis in renal transplant recipients

Introduction

Low-molecular-weight heparins are routinely used to prevent deep venous thrombosis following renal transplantation. Most low-molecular-weight heparins are sodium salts, but nadroparin is a calcium salt. Shortly after renal transplantation or during a rejection period patients may have an impaired renal function, hyperphosphataemia and hyperparathyroidism, which may provoke calcium-phosphate deposition.

Reports

Lareb received two reports on renal transplant patients with calcinosis cutis after treatment with nadroparin. Both patients are described in the referred publication[1].

Other sources of information

Literature

The two above-mentioned cases were presented in a publication by the reporters[1]. After development of the erythematous nodules with ulceration and necrosis, a technetium-99 bone scan was performed in one patient revealing spots at the sites of injection of nadroparin. In both patients a skin biopsy showed deposits of calcium in the collagenous and elastic tissue and vessel walls. After having developed a deep venous thrombosis the second patient received treatment with a sodium salt low-molecular-weight-heparin, which did not induce calcinosis cutis. Retrospectively, three other patients were considered to have had calcinosis cutis after treatment with nadroparin. After changing to sodium salt low-molecular-weight-heparin no such symptoms were observed.
Two other publications report calcium depositions in conjunction with renal impairment and the use of calcium heparin[2,3].

Databases

Calcinosis cutis can be coded as calcinosis, as any injection-site reaction and as application-site reaction. For the injection-site-related adverse events in the Lareb database see Table 1.

Table 1. Injection-site-related adverse events in the Lareb database

	Dalteparin B01AB04	Enoxaparin B01AB05	Nadroparin B01AB06	Tinzaparin B01AB10
calcinosis			2	
application-site reaction NOS	1	2		
injection-site bruising		2	1	
injection-site haemorrhage	1	4		
injection-site reaction NOS	1		3	1

Evaluation of these reports resulted in three reports with calcinosis cutis as characterised both by the description and the longer latency.

The WHO database contains only four reports on calcinosis and any heparin (see Table 2).

Table 2. WHO reports on any heparin and calcinosis

Sex, age	Heparin type	Onset	Outcome
F, unknown	enoxaparin	6 weeks after cessation	recovered with sequelae
F, 62	enoxaparin	20 days after start	recovered without sequelae
F, 35	nadroparin	7 days after cessation	recovered without sequelae
F, 58	nadroparin	4 weeks after cessation	recovered without sequelae

Mechanism

The reporting physicians classify the calcinosis cutis as a mix of the dystrophic and metastatic type. The injection trauma is regarded as the precipitating factor and the hyperparathyroidism and the raised calcium-phosphate product will have contributed to the calcium-phosphate depositions. Moreover, the calcium content of nadroparin may have contributed to an even higher local calcium-phosphate product, thereby provoking deposition of calcium phosphate.

Discussion and conclusion

Our reports and the additional diagnostic data in the reporters' publication suggest that the calcium content of nadroparin may have contributed to the calcinosis cutis in patients with risk factors like impaired renal function, hyperphosphataemia en hyperparathyroidism. A plausible pharmacological explanation is available.

References
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2. Fox JG, Walli RK, Simpson HKL. Calcified subcutaneous nodules due to calcium heparin injections in a patient with chronic renal failure. Nephrol Dial Transplant 1994;9:187-88.
3. Koch Nogueira PC, Giuliani C, Rey N, Said MH, Cochat P. Calcifying panniculitis in a child after renal transplantation. Nephrol Dial Transplant 1997;12:216-18.
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