Management of nadroparine calcium overdosing in elderly – a case report

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Introduction

We report on a 82 year old male patient who was treated with nadroparine calcium 7600 i.U. (= 0.8 ml) twice daily subcutaneously due to risk-associated acute pulmonary embolism (PE) and lower-extremity deep vein thrombosis (DVT) on both sides and who accidentally received a single 10 fold overdosage (8 ml = 76000 i.U., see figure 1) of anticoagulation four weeks after an osteosynthetic treatment of a fracture of the right ankle.

At that time, he was treated in another hospital. The accidental overdosage was recognized two hours after subcutaneous injection.

In medical history of the patient aoart from PE and DVT an arterial hypertension as well as dementia and and an orthopedic operation of the lower leg four weeks ago due to a collapse was known. There was no chronic renal failure, thrombophilia, coronary heart disease, ischemic stroke or history of bleeding known.

figure 1 – syringe with 8 ml = 76000 i.U. nadroparine calcium

Initial treatment and laboratory assessment

For further treatment and monitoring of the patient he was transferred to the emergency room (ER) of the departement of internal medicine. Due to the long period between application of nadroparine calcium and recognition of overdosage there was no liquid left to evacuate from the application area. The patient was conscious and in a haemodynamically stable condition (blood pressure: 123 / 80 mmHg; heart rate: 65 bpm) and had no clinical signs of bleeding.

Coagulation parameters including anti Xa-levels were analyzed to verify the overdosage and initially were checked every 90 to 120 minutes. We decided to give protamine after an analysis of coagulation parameters was performed 8 hours after overdosing. At that time activated partial thromboplastine time (aPTT) was 80 sec, international normalized ratio (INR) 1.50, thrombin time (TT) >240 sec and anti Xa-level 2.10 anti XaU/ml (aXa; normal range for peak level 3-4 hours after application 0.4-1.0 anti XaU/ml).

Therapeutic management

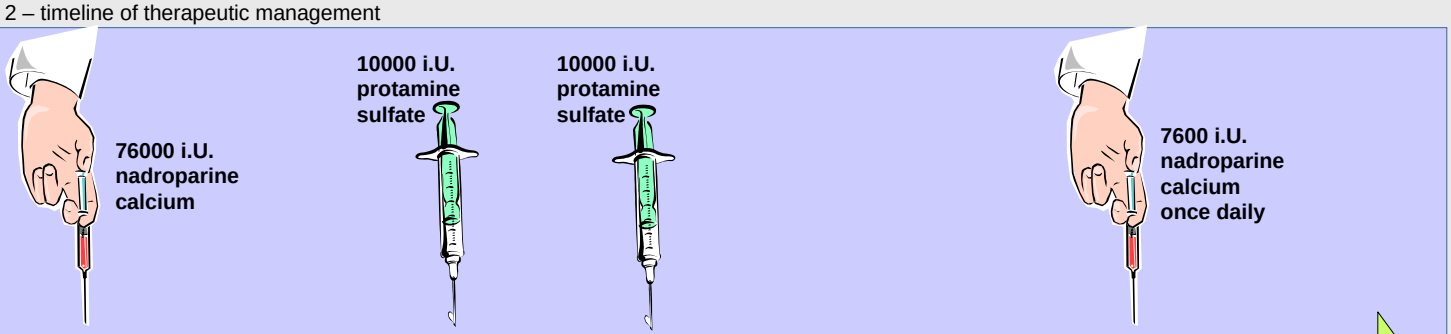
Due to age and medical history of the patient, we decided to partially antagonize nadroparine and applied protamine sulfate. The decline of nadroparine activity over time and the kinetics of protamine inactivation in relation to low-molecular weight heparine (LMWH) were calculated. We administered 10000 i.U. of protamine sulfate to antagonize approximately 16000 i.U. of the received 76000 i.U. of nadroparine, which were applied nine hours after the last injection, and coagulation assays were checked 30 minutes after protamine application. Coagulation parameters showed an initial good response. But 150 minutes after protamine application aPTT, TT and anti Xa- level increased again (see figure 2).

Therefore we decided to administer another 10000 i.U. of protamine. 30 minutes after the second protamine application coagulation parameters again decreased. No clinical signs of bleeding occurred so far. Monitoring of vital parameters showed stable conditions at all times. 180 minutes after the second protamine application TT increased again, but aPTT and anti Xa-levels remained stable. Due to the absence of any bleeding complications we refrained from a third protamine application. After monitoring over 24 hours without any clinical signs of bleeding, stable haemoglobin-test and decreasing coagulation parameters, the patient was transferred back to his ward (see figure 2).

Anticoagulant therapy was interrupted for another five days. As soon as the anti Xa-level was below the therapeutic range nadroparine was restarted with an reduced dose of 7600 i.U. once daily.

Until patient`s discharge from hospital no bleeding complications occurred.

figure 2 – timeline of therapeutic management



time after application of nadroparine	2 h 30 min	4 h 30 min	6 h	8 h	10 h	11 h	12 h	13 h	15 h 30 min	20 h 30 min	24 h **	123 h ***	221 h ****
aPTT [s]	33	64	75	80	52	63	68	51	63	68	51	30	
TT [s]		206	> 240	> 240	90	> 240	>240	66	182	> 120	111		
aXa-level [aXaU/ml]		1.77	1.90 *	2.10	1.76	1.70	1.96	1.48	1,56	1,40	1,38	0,05	0,46
Hemoglobin [g/dl]	12.9											13,2	12,1
Hematocrit [%]	39.2											39,9	37,5
Thrombocytes [/nl]	194											213	205
creatinine [mg/dl]	0.67											0.70	0.69
urea [mg/dl]	16											16	17
MDRD [ml/min/1,73cm²)]	113.6											108	109.8

* = 1:1-dilution with sodium chloride solution ; ** = end of monitoring ; *** = restart application of nadroparine calcium ; **** = conditions at discharge of patient

aPTT = activated partial thrombo-plastin time ; TT = thrombin time ; aXa level = Level of anti factor Xa-activity ; MDRD = Modification of Diet in Renal Disease

Conclusion

Fractional application of protamine sulfate in elderly is a save option to manage overdosing of low-molecular weight heparin, if coagulation parameters and clinical signs for bleeding are closely monitored.