Throbbing headache associated with enoxaparin administration: a case report, a review of pharmacovigilance databases for similar cases and possible mechanisms

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Enoxaparin is generally safe and well tolerated, but some safety studies have indicated the occurrence of side effects such as haemorrhages, anaemia, thrombocytopenia, allergies and skin problems (Laporte et al., 2014). Of the adverse drug reactions (ADRs) that have been identified and reported after the marketing of the drug, the incidence of headache is 'unknown' (Fox, 1999). Almost nothing is known about the relevance of this ADR in enoxaparin-treated patients.
In this study, we present a case of throbbing headache that appears to bear a 'certain' relationship with enoxaparin. A 60-years-old man experienced throbbing headache a few hours after the subcutaneous administration of this drug at therapeutic dose. Rechallenge on two other separate occasions separated by several days produced the same effect although with reduced intensity when the dose was lowered. Enoxaparin was replaced with warfarin and the patient no longer experienced headache attacks and remained headache-free during a 3-month follow-up.
The analysis of enoxaparin-induced headache in the American, Canadian and Australian pharmacovigilance databases have detected 1700 reports of headache related to active ingredients of ATC B01AB inserted from 1 January 2004 to 31 December 2012. More than 85% of the reports referred to heparin administration, 11% to enoxaparin.
Moreover a plausible pharmacological mechanism involved in ADR was provided. Heparin is involved in the suppression of the production of endothelin, the stimulation of the release of nitric oxide (NO) and the increase of cyclic guanosine monophosphate (cGMP) (Li at al., 1996; Yokokawa et al., 1993). NO donors are known to provoke an immediate headache in healthy individuals and in headache sufferers (Bagdy et al., 2010). Moreover, NO plays a role in processing sensory information and pain sensitization (Olesen J et al., 2008), stimulates from perivascular nerve fibres the release of calcitonin gene-related peptide (CRGP), (Messlinger et al., 2008) a potent vasodilator involved in the transmission of the pain.
In conclusion, physicians who prescribe this drug should be aware of this potential ADR. We suggest that it is a heparin class-effect, and therefore, a more general caution is also appropriate.

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