Clinical evaluation of pain during subcutaneous injections of low molecular weight heparins in healthy volunteers

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In order to compare the intensity and the duration of the pain following the subcutaneous injection of low molecular weight heparins, 0.4 ml nadroparin, 0.4 ml enoxaparin and 0.4 ml placebo (NaCl 0.9%) were administered at 1 week intervals to 12 healthy volunteers in a randomised, double-blind, three-period study. Pain was assessed by visual analogue and verbal category scales. Based on visual analogue scale scores, nadroparin resulted in significantly less pain than enoxaparin at 1 and 5 min after injection (6.2 ± 2.6 mm vs 21.9 ± 5.9 mm; $P < 0.05$ and 3.5 ± 1.5 mm vs 14.3 ± 4 mm; $P < 0.05$, respectively, mean $\pm$ s.e. mean). Similar results were obtained using verbal category scale. Confidence interval testing for difference between groups showed that nadroparin injection resulted in less pain than enoxaparin at 1 min (-15.8 : -31.2 to -0.4 mm).

Keywords low molecular weight heparin pain

Introduction

Subcutaneous injections of low molecular weight heparins may be painful for the patients. A preliminary study comparing the local tolerance of two low molecular weight heparins, calcium nadroparin and sodium enoxaparin in elderly patients, suggested that nadroparin was locally better tolerated than enoxaparin [1].

Methods

We performed a randomized, double-blind, three-period study in 12 healthy male volunteers in order to assess the intensity and duration of pain after a single subcutaneous injection of low molecular weight heparin. This study was approved by the local Ethics Committee and written informed consent was obtained from each volunteer. The volunteers, 21 to 34 years of age [mean $\pm$ (s.d.), 27 ± 5 years] received 0.4 ml nadroparin, 0.4 ml enoxaparin and 0.4 ml placebo (NaCl 0.9%) in a sequential mode according to a latin square design. In a given subject, each injection was performed at the same time of the day 1 week apart. After local disinfection with a non alcoholic detergent, the subcutaneous injections were performed, as

commonly recommended, by the same nurse throughout the three study periods. Visual analogue and verbal category scales were used to assess post-injection pain during 4 h (1 min, 5 min, 15 min, 30 min, 45 min, 1 h, 2 h, 3 h and 4 h after subcutaneous injection). The visual analogue scale consisted in a 100 mm horizontal line on which the subjects drew a mark corresponding to their pain level, the left and right extremity corresponding to the absence and to maximal pain respectively. The verbal category scale was a five-category scale which allowed the subjects to grade their pain as absent, slight, moderate, severe or extremely severe. The results of visual analogue scale were measured by the same investigator with the same ruler and the results of verbal category scale were quantified as no pain: 0, slight pain: 1, moderate pain: 2, severe pain: 3, and extremely severe pain: 4. We first performed an analysis for a latin square design [2] and when an overall significant F value ($P < 0.05$) was indicated, subsequent Scheffé's multiple comparisons test [3] was used to determine the significance of differences between treatment groups at each time point. The confidence intervals for between-group differences were calculated as mean of difference $\pm$ ($t \times$ standard error of mean), t used was corrected for multiple testing. The results are presented as mean $\pm$ s.e. mean.

Results

The upper panel of Figure 1 shows the time-course of pain evaluated by visual analogue scale. 1 and 5 min after subcutaneous injection, nadroparin resulted in significantly less pain than enoxaparin [6.2 ± 2.6 mm vs 21.9 ± 5.9 mm ($P < 0.05$) and 3.5 ± 1.5 mm vs 14.3 ± 4 mm ($P < 0.05$) respectively]. Placebo produced an intermediate level of pain. Confidence interval testing for differences between treatment groups confirmed that nadroparin was significantly less painful than enoxaparin at 1 min (see Table 1). However, changes at 5 min did not reach statistical significance.

The lower panel of Figure 1 shows the time-course of pain evaluated by verbal category scale. 1 and 5

Table 1 95% confidence intervals and mean values (mD) for differences in intensity of pain assessed by visual analogue scale

Time (min)	Nadroparin – enoxaparin (mm)	Enoxaparin – placebo (mm)	Nadroparin – placebo (mm)
1	-31.2 to -0.4*	-5.1 to 17.5	-20.1 to 0.9
mD	-15.8	6.2	-9.6
5	-22.4 to 0.8	-1.0 to 19.4	-11.1 to 7.9
mD	-10.8	9.2	-1.6

* Confidence intervals which do not include zero indicate a significant difference between the compounds.

Figure 1 Time-course of pain after single subcutaneous injection of enoxaparin (○), nadroparin (■) and placebo (△) determined by two methods: visual analogue scale in mm (upper panel) and verbal category scale (0: no pain, 1: slight pain, 2: moderate, 3: severe, 4: extremely severe) (lower panel). (mean $\pm$ s.e. mean; * : $P < 0.05$ vs nadroparin).

min after subcutaneous injection, nadroparin resulted in significantly less pain than enoxaparin [0.67 ± 0.25 vs 1.42 ± 0.23 ($P < 0.05$) and 0.33 ± 0.19 vs 1.00 ± 0.22 ($P < 0.05$) respectively]. There was no significant difference between nadroparin and placebo. Five minutes after subcutaneous injection, placebo induced less pain than enoxaparin (0.33 ± 0.19 vs 1.00 ± 0.22 ; $P < 0.05$).

Discussion

In this single dose study, the pain associated with subcutaneous injections of nadroparin was significantly less pronounced than with enoxaparin during the 5 min following injection. These results support the conclusions of the uncontrolled open clinical trial performed by Albanese *et al.* [1] and previous report of a better local tolerance of calcium vs sodium unfractionated heparin [4]. This advantage cannot be attributed to the absence of a stabilizer in nadroparin, since both solutions of low molecular weight heparins are free of adjuvant. Also the molecular weight of both compounds is identical (4500 daltons). One possible explanation for the difference we have found could be with the cationic salt composition of these preparations, nadroparin being a low molecular weight heparin salified with calcium (3.8 mg in 0.4 ml), whereas enoxaparin is a low molecular weight heparin salified with sodium (4.8 mg in 0.4 ml). Indeed, pain intensity increased with the sodium concentration and was important with enoxaparin (4.8 mg), intermediate with 0.4 ml of NaCl 0.9% (3.6 mg) and slight with nadroparin (0 mg).

It should be stressed that the pain levels experienced by our normal volunteer subjects remained low. This can be seen from the pain scores on both the visual analogue and the verbal category scales. Also, the comparisons that were significant on confidence interval testing were borderline. Thus in spite of the statistically significant difference we found between nadroparin and enoxaparin, the clinical significance of our results remains uncertain. It is unlikely that our results may be extrapolated to patients following the first subcutaneous injection of enoxaparin and nadroparin. However further studies are required to determine whether similar results can be found during repeated administration of enoxaparin and nadroparin in patients.

In summary, under the experimental conditions of this study in 12 healthy volunteers, subcutaneous injections of nadroparin were significantly less painful than enoxaparin. The presence of sodium in enoxaparin but not in nadroparin could explain our results. If they are confirmed during repeated administration, it may be recommended to preferentially use a calcium salt of low molecular weight heparin in order to decrease pain intensity.

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