the lack of difference between the groups. Overall, it remains to be elucidated whether the group differences observed by Schoenhofer et al\(^1\) were due per se to the effects of immersion.

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References


To the Editor:

We thank Dr. Leal and colleagues for their interest in our article. In response to their questions we can report that, although we did not measure it specifically, the time from immersion to measurement was similar for patients and control subjects (typically 15 min). The swimming pool temperature was 27°C. Although this is less than is recommended by Leal et al, it was of course the same for patients and control subjects. Likewise, although it might have been better to use the seated erect position both in and out of the pool, we did not consider this to the practical, so patients in the pool were studied erect and straight. Since this was not the same for patients and control subjects, we doubt that this influenced our results.

Finally, in our article we acknowledged that the difference in maximum inspiratory pressure (Pmax) between patients and control subjects just failed to reach the 0.05 significance level. We believe that the small number of enrolled patients may be associated with a type II error. Nevertheless, based on clinical criteria, our control subjects were healthy; therefore, if anything, this serves to support our conclusion that the differences in Pmax between the groups are due to respiratory muscle weakness.

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Postbronchoscopy Fever in Patients With Nontuberculous Mycobacterial Lung Disease

To the Editor:

We read with great interest the report by Um et al (March 2004)\(^1\) on the incidence and risk factors of postbronchoscopy fever. They showed that fever developed in 7 of 48 patients (15%) with pulmonary tuberculosis, and pulmonary tuberculosis was the independent risk factor for postbronchoscopy fever. Interestingly, fever did not develop in 13 patients with positive nontuberculous mycobacteria (NTM) culture findings.\(^1\)

The incidence of postbronchoscopy fever has not been well studied in patients with NTM lung disease. We recently performed a study\(^2\) to determine the frequency of NTM infection in 105 patients with bilateral bronchiectasis and bronchiolitis at chest CT. Bronchoscopy was performed in 43 patients (41%). NTM diseases were diagnosed in 25 of these 43 patients (58%) [\textit{Mycobacterium avium} complex in 12 patients, \textit{Mycobacterium abscessus} in 11 patients, and others in 2 patients].

Postbronchoscopy fever developed in 15 patients (43%). The incidence of fever was 48% (12 of 25 patients) in those with NTM disease. NTM disease was more common in the fever group (12 of 15 patients, 80%) than in the nonfever group (13 of 28 patients, 46%)\(\ [p = 0.0047]\). Bacteremia was not found, and the fever subsided spontaneously within a day in all patients.

BAL was performed in 23 patients (92%), and transbronchial lung biopsies were performed in 20 patients (80%) with NTM disease. BAL or bronchial washing fluid smears were positive for acid-fast bacilli in 12 patients (48%) with NTM disease. The high incidence of postbronchoscopy fever in our patients with NTM disease was partially explained by these findings.

Elevated cytokines, such as tumor necrosis factor-\(\alpha\) and interleukin-1\(\beta\), in BAL fluid might be responsible for postbronchoscopy fever in patients with pulmonary tuberculosis, as Um et al\(^1\) suggested. This may be also true in patients with NTM disease. Some reports\(^3\),\(^4\) revealed that many proinflammatory cytokines, such as tumor necrosis factor-\(\alpha\), interleukin-1\(\beta\), interleukin-6, and interleukin-8, were increased in BAL fluid in patients with NTM disease. In summary, the high incidence of postbronchoscopy fever in patients with NTM lung disease may be related to the diagnostic techniques during bronchoscopic procedures, clinically advanced disease, or the release of pyrogenic cytokines, as well as pulmonary tuberculosis.

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References

Dose Capping Enoxaparin Is Unjustified and Denies Patients With Acute Coronary Syndromes a Potentially Effective Treatment

To the Editor:

We read with interest the article from Macie et al (May 2004) highlighting the importance of adhering to the correct dosing of enoxaparin for the prevention of ischemic events in patients with unstable angina or non–ST-segment elevation myocardial infarction. The article adds to the current controversy over dosing practices for enoxaparin in obese patients, while discussing the risk factors for increased bleeding. We would like to add the following points:

The optimal dose of enoxaparin for treatment of acute coronary syndromes (ACS) is 1 mg/kg, and this dose should be adhered to—ie, no more and no less. There is evidence that when the dose is adjusted down unnecessarily, survival and efficacy is reduced, thus emphasizing the importance of a correct dosing regimen.

There is evidence that the 100-mg capped dose used in this study is unnecessary, both in terms of the pharmacokinetics of enoxaparin in obese volunteers and its safety and efficacy in ACS patients. In fact, there is no evidence to suggest the need to modify the currently recommended dose of enoxaparin for treatment of venous thromboembolism and ACS in obese patients. The 100-mg capped dose applicable in Canada goes against all known data, arising from a demand from the Canadian Health Authority that is supported by neither clinical trial data nor the recommendation of the manufacturer. We can only speculate as to the rationale behind this labeling requirement. When the effect of low-molecular-weight heparin (LMWH) in protecting against new cardiac events in unstable coronary artery disease (CAD) was looked at, the Fragmin During Instability in Coronary Artery Disease study group capped the dosage of dalteparin at 10,000 IU and dalteparin was the first LMWH licensed in Canada for ACS. However, because different LMWHs have different pharmacologic profiles and recommended doses, the results obtained with one LMWH preparation should not be extrapolated to another. It is interesting to note that the subsequent Fragmin in Unstable Coronary Artery Disease Study trial had no mention of a capped dose and used a patient-weight range > 150 kg.

It was stated in the article by Macie et al that previous randomized controlled trials (RCTs) have limitations in addressing practical issues that may impact on bleeding risk in the real-world population, because of the exclusion of patients weighing > 100 kg. First, the prespecified definition of obesity should use body mass index (BMI), because body weight alone is not always an accurate reflection of obesity. For example, the heaviest weight recorded in the Thrombolysis in Myocardial Infarction (TIMI) 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) databases for a nonobese patient is 110 kg. Second, it is untrue that other studies have not researched patients weighing > 100 kg: in the meta-analysis of the TIMI 11B and ESSENCE trials comparing the safety and efficacy of a weight-adjusted dose of enoxaparin and unfractionated heparin (UFH) in obese patients (n = 7,081), approximately 26% of patients in the trial were obese (defined as BMI ≥ 30), thereby providing a large sample size for comparison. The maximum weight of patients treated with enoxaparin in this meta-analysis was 158.6 kg. Of these patients, 540 patients weighed > 100 kg (n = 275 UFH, n = 265 enoxaparin). Statistical analysis on this subgroup showed no significant difference between the UFH and enoxaparin groups in either the double or triple end points (incidence of death and myocardial infarction and/or urgent revascularization). Meanwhile, the maximum weight of patients in the Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial, which evaluated the effect of enoxaparin and UFH on death and myocardial infarction in high-risk patients presenting with non–ST-segment elevation ACS (n = 10,027), was 175 kg in the UFH group and 196 kg in the enoxaparin group, while the interquartile range was 70 to 91 kg for both groups—the highest weights for any ACS trial to date. There were no inclusion/exclusion criteria related to weight, and dosing was 1 mg/kg for all patients. Recent preliminary results from the SYNERGY trial have shown no evidence of differing efficacy or safety between 1 mg/kg weight-adjusted enoxaparin and UFH in the obese subgroup (K.W. Mahaffey, MD; personal communication; September 24, 2004). To our knowledge, there has only been one clinical trial of enoxaparin in patients with ACS where there was a weight cutoff at 110 kg. Third, the studies referenced for this statement are a pharmacodynamic study of tinzaparin and a pharmacokinetic study on the effect of weight and LMWH in the treatment of venous thromboembolism (ie, no ACS patients).

In the study by Macie et al, the authors report that increased length of treatment was related to bleeding: one should question whether incorrect dosing also impacted on bleeding and whether this was tested in the bleeding risk model. For instance, what was the incidence of major bleeding in the 17 patients who received a dose > 1 mg/kg? It is also important to note that the major bleeding definition used by Macie et al was less stringent than that used in TIMI 11B and ESSENCE—with the definition in the study by Macie et al including a hemoglobin drop of 20 g/L in place of 30 g/L. It is therefore difficult to compare bleeding rates, because one could expect rates to be higher in the study by Macie et al compared with the RCTs.

When “any bleeding episode” is recorded as a safety end point, subcutaneous administration in obese patients is expected to cause a higher incidence of ecchymosis and hematoma (at the injection site) compared with IV administration. In a real-world setting—an analysis of 13,231 ACS patients in the Global Registry of Acute Coronary Events (GRACE)—major bleeding rates have been reported to be 2.1% in patients receiving a LMWH (of which 80.1% received enoxaparin) vs 4.9% in those receiving UFH.

With regard to the reported risk factors that increase bleeding risk with enoxaparin, advance age and renal insufficiency have also been reported in GRACE to be independent predictors of bleeding, ie, independent of LMWH use. Dose adjustment of the standard of 1 mg/kg qd dose of enoxaparin is recommended by the manufacturer in patients with severe renal impairment (creatinine clearance < 30 mL/min), because enoxaparin is renally cleared (according to the prescribing information of the

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