

The effect of different nitrate preparations on plasma heparin concentrations and the activated partial thromboplastin time

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Summary: There is evidence that intravenous nitrates which are frequently used in acute coronary syndromes may interfere with the anticoagulant effect of heparin. We compared the effect of two different nitrate preparations on the activated partial thromboplastin time (APTT), anti-thrombin III activity (AT III) and plasma heparin levels in patients ($n = 50$) undergoing routine percutaneous transluminal coronary angioplasty (PTCA) for stable angina. Patients were randomized to either: (1) intravenous heparin and nitroglycerine (GTN); or (2) intravenous heparin and isosorbide dinitrate. The APTT, plasma heparin concentration and AT III activity were measured before PTCA and at 2 and 4 hours after commencement of infusions. Both groups received identical doses of heparin. Group 1 patients received a constant dose of 16.6 $\mu\text{g}/\text{minute}$ of GTN, and group 2 patients received 33.3 $\mu\text{g}/\text{minute}$ of isorbide dinitrate.

At 4 hours the median APTT ratio was significantly lower in group 1 compared with group 2 (2.6 versus 4.5) ($P < 0.05$) as was the plasma heparin concentration (0.18 U/ml versus 0.32 U/ml ($P < 0.05$)). However, no significant difference in APTT ratios or plasma heparin concentrations were noted at any of the other sample times. AT III activity was not significantly different between the groups at any sample time. Within-group analysis showed significantly lower APTT ratio and heparin concentrations at 4 hours compared with the respective 2 hour values.

These results would suggest that there is a potential impairment of anticoagulation with low-dose intravenous nitroglycerine and to a lesser extent with low-dose isosorbide dinitrate. Early and frequent monitoring may therefore be appropriate when intravenous nitrates and heparin are used in combination.

Introduction

Intravenous nitrates and heparin are frequently prescribed together in acute cardiac conditions and following percutaneous transluminal coronary angioplasty (PTCA). Previous reports suggest that high-dose intravenous nitroglycerine may adversely influence the anticoagulant effect of heparin.⁴⁻⁷ Although there is some evidence suggesting that oral isosorbide dinitrate does not interfere with heparin the anticoagulant activity of heparin,⁸ there is no information comparing the effects of intravenous nitroglycerine and intravenous isosorbide dinitrate on the anticoagulant action of heparin. We have therefore compared the effects of low-dose intravenous nitroglycerine (GTN) and isosorbide dinitrate (Isoket) on the anticoagulant effect of heparin by serial measurements of the activated partial thromboplastin time (APTT), plasma heparin concentration and anti-thrombin (AT) III activity in two groups of patients receiving nitrates and heparin routinely after PTCA.

Methods

Patients

All patients with stable angina admitted for routine PTCA were considered for entry into the study. This study population allowed us to use a group of patients who would routinely receive a combination of low-dose intravenous nitrates and intravenous heparin after the procedure. Patients were excluded if they had a history of bleeding disorder, were taking oral anticoagulant therapy, or had hepatic or renal impairment. They were also excluded if they had received thrombolytic therapy within 2 weeks of the procedure. Informed consent was obtained from all patients who participated in the study.

At the start of the PTCA all patients received a bolus of 10,000 U of heparin intravenously as part of the routine PTCA procedure. Following a successful procedure patients were randomized to receive either intravenous heparin plus GTN (group 1) or intravenous heparin plus Isoket (group 2).

The infusions were commenced immediately on return to the ward and all intravenous solutions were given through non-absorbable tubing. The heparin used for this study was 'Pump-Hep' (Leo Laboratories), containing 1,000 U/ml of heparin in normal saline. Group 1 patients received Tridil (Du Pont Pharmaceutical); 1 ml containing 5 mg of nitroglycerine in 30% alcohol; 30% propylene glycol and sterile water; whilst group 2 patients received Isoket (Schwartz) 0.1% containing 1 mg/ml of isosorbide dinitrate in sterile isotonic saline (no preservatives). The starting dose of heparin for both groups was 1,000 U/hour. The rate of nitroglycerine and isosorbide dinitrate infusions remained constant throughout the sampling times. Patients were withdrawn from the study if either heparin or nitrate infusions were stopped for any reason. In our unit the APTT is routinely measured at 6 hours post commencement of infusions and the heparin dose adjusted to maintain an APTT of greater than twice control. Therefore the 2 and 4 hour samples were not subjected to routine dose adjustments. Infusions of nitrates and heparin were continued for 24 hours.

Venous blood sampling was from a large antecubital vein with minimal stasis. All the samples were analysed blind of patient grouping by the technical staff of our haematology department. Blood was taken into 0.019 M trisodium citrate anticoagulant and was assayed immediately to obtain APTT ratios, plasma heparin concentrations and AT III activity. Samples were obtained before PTCA and at 2 and 4 hours after the onset of infusions.

Commercially available radioimmunoassay kits were used for determining plasma heparin concentrations (Rotachrom) and AT III activity (Stachrom). APTT ratios were performed by laboratory staff using standard techniques.

Statistical analysis

A non-parametric method of analysis (Mann-Whitney *U*) was used for determining the significance in the differences in APTT ratios and plasma heparin concentrations between the groups at the sampling times, and a Wilcoxon (signed rank) test was used to compare the difference in APTT ratios and heparin concentrations within each group. A *P* value of < 0.05 was considered to be statistically significant.

Results

Fifty patients undergoing routine PTCA for chronic stable angina were entered into the study. Five patients from group 1 (GTN) were withdrawn as a result of clinically significant hypotension occur-

ring within 2 hours of commencing the infusions. One patient in group 2 was also withdrawn owing to hypotension. A further three patients in group 2 were withdrawn because bleeding around the indwelling femoral artery sheath required temporary cessation of the heparin infusion. Emergency coronary surgery was needed for one patient in group 2 during the study period who was also withdrawn. Three further patients in group 2 were withdrawn owing to sampling errors (incorrect sample tubes, samples analysed too late or samples omitted).

As a result of the withdrawals, 33 men and four women remained in the study, mean age (s.d.) group 1 (*n* = 20) 54 years (7), group 2 (*n* = 17) 56 years (8). The use of concomitant drug therapy did not differ between the two groups. Intravenous heparin and nitrate infusions were started at a mean of 17 minutes after the initial heparin bolus in group 1 and 19 minutes in group 2. The dose of intravenous heparin received by the two groups at the sample times is shown in Table I. The dose of intravenous GTN received by group 1 patients was 16.6 µg/minute and the dose of isosorbide dinitrate received by group 2 patients 33.3 µg/minute. Despite both groups having received identical doses of heparin at the sample times there was a significantly lower median APTT ratio at 4 hours in group 1 compared with group 2 (2.6 versus 4.5) *P* = 0.03 (95% confidence interval - 2.05 to - 0.1) (Table I). There was no significant difference in APTT ratios at pre- and 2 hour-sampling times between the groups (Table I). The lower APTT ratio was reflected by a significantly lower plasma heparin concentration at 4 hours in group 1 compared to group 2 (0.27 U/ml versus 0.32 U/ml), *P* = 0.02 (CI - 0.55 ± - 0.03) (Table I). The heparin concentrations at the other sampling times did not differ significantly between groups. At no sample times were there any significant differences in AT III activity.

Analysis within each group showed that in both groups the APTT ratios at 4 hours were significantly lower than their respective 2 hour values despite a constant infusion of heparin. Again this was reflected by lower plasma heparin concentrations at 4 hours compared to 2 hours.

Discussion

There is still some controversy concerning a potential interaction between intravenous nitroglycerine and heparin. While a number of reports^{4-6,9} claim an interaction several authors disagree.¹⁰⁻¹² The debate was focused on intravenous nitroglycerine but one study has suggested that there is no adverse interaction when oral isosorbide dinitrate is given in combination with intravenous heparin.⁸ In view of the existing controversy over the effects of

Table I Results of median (interquartile ranges) APTT ratios, median plasma heparin concentrations and mean (s.d.) AT III activity at pre, 2 and 4 hour sample times for groups 1 (nitroglycerine) and 2 (isosorbide dinitrate)

	Group 1 (n = 20)	Group 2 (n = 17)
Mean age (s.d.)	54 (7)	56 (8)
Heparin dose (U/hour)		
2 hours	1,000	1,000
4 hours	1,000	1,000
APTT ratio		
Pre	0.9 (0.88–1.06)	0.9 (0.87–0.98)
2 hour	4.4 (3.6–4.7)	4.6 (4.5–4.7)
4 hour	2.85 (1.8–4.2)*	4.5 (2.79–4.7)*
Heparin level (U/ml)		
2 hour	0.27 (0.19–0.5)	0.46 (0.23–1.05)
4 hour	0.18 (0.12–0.31)**	0.32 (0.2–0.86)**
AT III (% activity)		
Pre	95.5 (14)	92 (16)
2 hour	89.9 (16)	89 (19)
4 hour	84.7 (15)	83.3 (17)

* and ** $P < 0.05$.

nitroglycerine and the lack of comparative data with other nitrates, we felt that there was a need to address this issue since both intravenous nitroglycerine and isosorbide dinitrate are frequently given in combination with heparin in routine clinical practice.

Recently we reported on the effects of nitroglycerine on plasma heparin concentrations, with the APTT ratio and heparin concentrations being significantly lower at 4 hours post commencement of infusion than the 2 hour values in the group receiving nitroglycerine an effect not seen in the control group who received intravenous heparin alone.⁹ In the present randomized study the 4 hour APTT ratios and heparin concentrations were significantly lower than their respective 2 hour values for both nitrate preparations. Possible explanations to account for this include a diminishing anticoagulant effect of the heparin bolus by 4 hours or acceleration of heparin elimination by both nitrate preparations. Interestingly, the median APTT ratios and plasma heparin concentrations at 4 hours were significantly lower in group 1 (intravenous nitroglycerine) compared with group 2 (intravenous isosorbide dinitrate). This would imply that either nitroglycerine or one of its metabolites is somehow interfering with the anticoagulant effect of heparin to a greater extent than isosorbide dinitrate and its metabolites.

From our results it would appear that this phenomenon does not occur secondary to a reduction in AT III activity, as has been postulated by others.⁷ The methodology varies markedly between our study and the one by Becker *et al.*, the most important difference being the higher dose of

nitroglycerine used (175–883 $\mu\text{g}/\text{minute}$). Possible mechanisms by which the plasma heparin level is reduced by nitroglycerine (and to a lesser extent isosorbide dinitrate) include nitroglycerine forming complexes with plasma proteins, producing a protamine-like effect by neutralization of the acidic heparin. Alternatively, metabolites of nitroglycerine may possibly interfere with heparin metabolism or elimination either directly or indirectly. We have shown using cultured human endothelium cells that nitroglycerine does not affect cellular uptake or release of heparin implying that this is not the mechanism involved.¹³ In a previous study⁹ we determined that the platelet factor four (PF4) levels were unaffected by nitroglycerine so it is unlikely that nitroglycerine is increasing PF4 levels which has an anti-heparin effect.

Although in this study the nitrate doses used were not titrated to a specific end point, such as a specific fall in systolic blood pressure, they represent doses that are currently used routinely in our unit post PTCA and were thus felt to be clinically more relevant. The dose of nitrates used were equivalent in terms of potency. Nitrate levels were not assayed at the sample times since these are not readily available, and the doses used were chosen for similar clinical effect, not similar plasma levels, which we feel to be less relevant. A control group, not receiving nitrates, was not used since the primary aim of the study was to compare the effects of two different nitrate preparations, on the anticoagulant effect of heparin. Previous work by ourselves has compared the intravenous effect of GTN with a control group not receiving any nitrate formulation.⁹

Intravenous nitrates are commonly given to patients with acute cardiac conditions in combination with heparin. It is important to be aware of a potential impairment of effective anticoagulation that seems to occur with nitroglycerine (and to a lesser extent with isosorbide dinitrate). Therefore frequent and early monitoring of the APTT is advised when intravenous nitrates and in particular

nitroglycerine are used in combination with heparin.

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