CORRESPONDENCE

Heparin Nitroglycerin Interaction

To the Editor—Resistance to the anticoagulant effect of heparin rightly concerns all anesthesiologists who administer the drug intravenously. Recently, an interaction between heparin and nitroglycerin (NTG) has been described in the medical literature. This interaction has been reported in at least three studies. Col et al. were the first to describe this drug interaction and studied it in vitro by examining the effect of heparin and NTG or propylene glycol on the aPTT. They described a decreasing clotting time associated with increasing concentrations of NTG or propylene glycol. They also examined this interaction in vivo in five normal subjects by measuring the effect on the aPTT of the injection of heparin 30 IU/kg alone (control) and mixed in a syringe with NTG 0.2 ml (0.3 mg) or its diluent propylene glycol 0.2 ml. At 30 min there was a 70% reduction in aPTT with heparin and NTG, and a 49% reduction with heparin and propylene glycol. A further investigation in a group of eight patients with coronary disease, treated with IV NTG infusing at 50 μg/min (0.33 ml/min propylene glycol), revealed similar results. Two hours after the initiation of the NTG infusion, heparin 30 IU/kg was injected intravenously, and 30 min after that injection the aPTT was measured. The aPTT increased to 66 ± 7 s, which was only 61% of the increase obtained with this dose of heparin in normal subjects (P < 0.05).

Habbbad and Haft examined whether this resistance to heparin was present with simultaneous NTG and heparin infusions. In a study of seven patients, their observations, presented graphically, indicated that an increase in the infusion rate of NTG causes the aPTT to decrease in spite of a constant heparin infusion rate. Conversely, slowing the NTG infusion led to an increase in aPTT. These effects were seen regardless of whether propylene glycol was included in the preparation. Though their results were not subjected to statistical analysis they concluded that the addition of NTG and not propylene glycol is responsible for heparin resistance.

Pizzulii et al. conducted a clinical study with patients receiving simultaneous heparin and NTG infusions. In this study the heparin infusion was titrated to achieve an aPTT > 100 s then while continuing to infuse heparin, NTG was begun intravenously at 2–5 mg/h. During these simultaneous infusions aPTT decreased significantly from 130 ± 28 s to 60 ± 23 s (P < 0.01). Following termination of the NTG infusion the aPTT returned to the initial value (195 ± 30 s). In nine of the 27 patients studied, heparin concentrations were also measured. Interestingly, the heparin concentration found during infusion of heparin alone (0.31 ± 0.1 IU/ml) was unchanged from the heparin concentration discovered during concurrent infusion of NTG and heparin (0.28 ± 0.18 IU/ml), leading these investigators to conclude that the NTG induced a reversible heparin resistance. They recommended adequate testing of aPTT and appropriate adjustment of heparin infusion whenever NTG is simultaneously being infused.

Due to the increasing number of intravascular and surgical procedures that require the concomitant use of parenteral heparin and NTG we believe this newly reported drug interaction has obvious importance to all practicing anesthesiologists and is worthy of further investigation.

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REFERENCES

Effects of Nitrous Oxide on Rat Embryos Grown in Culture

To the Editor—We previously reported that “the rat whole embryo culture system” is a useful in vitro model for studying the mechanisms of nitrous oxide (N₂O) teratogenicity. The system that we described involved explanting embryos on the morning of gestational day 10 (early organogenesis stage; approximately 10 somites), and culturing them in an atmosphere of 75% N₂O for 22 h. Morphologic and biochemical abnormalities were seen. The reviewers of the paper correctly commented, however, that the total number of morphologic abnormalities (7/54) among N₂O exposed embryos was only just different (P = 0.02) from controls (0/46). Furthermore, specific types of abnormalities were present in too few a number to be statistically significant. We have now performed additional experiments which demonstrate that rat embryos are more sensitive to the adverse effects of N₂O when exposed on gestational day 9. Specifically, we cultured embryos in an atmosphere of 50–75% N₂O for 24 h starting on the morning of day 9 (early somite stage; 0–1 somites), and we have found that when examined on day 11 there was a highly significant increase in malformations, in general, and in left-sided tail and inverted heart, in particular (table 1). These results, together with the decreased protein content in embryos exposed to N₂O on day 9 (table 1), provide more