Preoperative Intravenous Nitroglycerin: A Potential Complication for Cardiopulmonary Bypass

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Abstract

***(J. Extra-Corpor. Technol.* 19[3] p. 369–371 Fall 1987, 13 ref.) It has been reported that intravenous nitroglycerin may interfere with the anticoagulation effect of heparin.[1] A literature search reports this only in low dose heparin management for coronary care unit patients. We have observed this same effect but on a much larger scale with complete heparinization required for cadiopulmonary bypass. We began to observe an inadequate response to the calculated dose of heparin approximately one year ago (400 units/kg.). Some adult patients required as much as four times the calculated dose of heparin to achieve an activated clotting time of greater than 600 seconds.**

Preoperative PTT and AT3 levels and postoperative levels were obtained on 25 adult patients. These tests yielded normal values and we then expanded our investigation. A systematic breakdown of medications administered to patients preoperatively was begun, checking for potential heparin neutralization. The studies of the medications administered revealed nitroglycerin to be the only common denominator for all the patients that required large heparin doses.

Many coronary artery bypass patients at our institution are placed on intravenous nitroglycerin prior to surgery. Our search of the literature revealed this to be a previously unreported potential complication for cardiopulmonary bypass in patients on high dose intravenous nitroglycerin.

Introduction

Nitroglycerin—a drug of obvious benefit to the patient with impaired coronary function. Heparin—a drug absolutely necessary for the function of extracorporeal circulation. Combined—a potential for increasing the complications of cardiopulmonary bypass to unacceptable levels.

Nitroglycerin was first synthesized by Sobrero in 1846. Constantin Hering, in 1847, developed the sublingual dosage form for nitroglycerin, which he advocated for a number of diseases. In 1857, Brunton administered amyl nitrite, a known vasodepressor, by inhalation, and he noted that anginal pain was relieved within 30 to 60 seconds. In 1879, William Murrell established the use of sublingual nitroglycerin for relief of the acute anginal attack and as a prophylactic agent to be taken prior to exertion. The empirical observation that organic nitrates could be used safely for the rapid and dramatic alleviation of the symptoms of angina pectoris led to their widespread acceptance by the medical profession.[2]

For over a century, nitroglycerin has been known to be useful to prevent or relieve acute anginal attacks. Intravenous infusion of nitroglycerin in patients with acute myocardial infarction at doses that maintain or improve stroke work can relieve pulmonary congestion by decreasing left ventricular filling pressure; there is also a reduction of myocardial oxygen demand.[3]

Although the mode of action of organic nitrates to relieve typical angina is not fully understood, the preponderance of evidence favors a reduction in the myocardial requirement for oxygen as the major action. The ability of nitrates to dilate large coronary vessels selectively may be the primary mechanism by which they benefit patients with angina caused by coronary spasm.

In 1916, the medical student McLean made the serendipitous finding of a phospholipid anticoagulant. Soon thereafter, heparin, named because of its abundance in liver, was discovered by Howell (1922), in whose laboratory McLean had been working.[4] Today commercial heparin is prepared from bovine lung and

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porcine intestinal mucosa, but it can also be obtained from sheep and whales.[5]

When injected intravenously, heparin has two major pharmacological effects—impairment of blood coagulation and reduction of the concentration of triglycerides in plasma. The anticoagulant effect of heparin is essentially immediate. Heparin acts indirectly by means of a plasma cofactor, antithrombin III.

Antithrombin III forms irreversible complexes with thrombin, and as a result, both proteins are inactivated.[6] Heparin markedly accelerates the velocity, but not the extent, of this reaction.[7] A ternary complex is apparently formed between heparin, antithrombin III, and the clotting factors.[8] Heparin is metabolized in the liver by an enzyme termed heparinase, and the inactive metabolic products are excreted in the urine.

Patient Population

Twenty-five consecutive adult patients, twenty-four males and one female, were evaluated for possible dysfunction of the calculated heparin dose (400 units/kg.). Fifteen patients (60%) required multiple doses of heparin, ranging from a total dose of 800 units/kg. to 1400 units/kg. to bring the ACT to approximately 600 seconds. Control values of ACT ranged from 120 to 140 seconds.

Methods and Observations

Measurement of heparin effect is performed by use of ACT method. ACT has been recommended as the best and quickest measurement of anticoagulation for cardiopulmonary bypass by numerous investigators.[9,10,11] Recommended range of ACT has been reported as 400–600 seconds[12] after heparinization. ACT method is performed by use of Hemochron 400 and celite activated test tubes[a]. Backup method is performed by use of Temp-Blok Module Heater[b] and Siliceous Earth Test tubes[c] (manual method).

It has been our experience in approximately 2,000 patients that an ACT of 600 seconds provides adequate heparinization for four hours of extracorporeal circulation without need of additional heparin. Reversal of heparin is at the ratio: 1 mg of protamine/100 units heparin. This returns the ACT to control value with approximately plus or minus 10%.

Our observations began by realizing some patients required multiple doses of heparin for ACT to equal 600 seconds. Our first reaction was to question the method of heparin administration. The second step was to change lots and manufacturers of heparin. These changes yielded no benefit. All drugs administered and preoperative procedures affecting the patients were recorded.

A literature search was performed looking for drugs that inhibit heparin action. This revealed nothing in relation to our patients. All high base drugs were then evaluated as possible neutralizers of (acid) heparin. For example, the phosphate enema was changed to saline type.

Platelet counts preoperatively were measured. High platelet concentration had been reported to effect heparin action.[13] Platelet counts were within normal range. Since heparin works with antithrombin III these levels were measured and found to be within normal range. Also, PT and PTT levels were measured preoperatively and intraoperatively and found to be normal before heparin administration, but not within the range to be expected after heparin. The important factor was that not every patient required larger than normal doses of heparin. The age, weight, sex, and type of surgery was then compiled for adult patients.

The realization came that the problem was related only to coronary artery bypass procedures, but not all of these procedures experienced heparin resistance.

Our coronary artery bypass patients are normally placed on IV nitroglycerin for 12 hours preoperatively. Infusion is at 10 drops per hour increasing to 30 drops per hour as arterial pressure allows (50mg./250 D5W).

The patients requiring large doses of heparin were the same patients that received large doses of nitroglycerin (30 drops per hour for a longer time).

The cause of the heparin neutralization is not yet understood but we deduct the effect is caused by nitroglycerin. This risk seems to be totally dose related, and, therefore, a threshold must be reached before the effect is seen.

Perhaps one of the most interesting facts of this observation is that an adequate protamine dose given for reversal of heparin equals the initial calculated dose based on 400 units per kg. of heparin. This lends thought that the neutralization of the additional heparin is nonreversible, as we have not observed heparin rebound in our patients.

Conclusion

Our findings indicate that there is a definite relation between intravenous nitroglycerin and heparin resistance in the clinical setting.

Currently, all patients at our institution who have received nitroglycerin are administered 500 units heparin per kg. as the initial dose. In the majority of patients this is enough to bring ACT to greater than 400 seconds, but not to 600 seconds.

a International Technidyne Corporation, Edison, NJ 08820
b American Hospital Supply, McGaw Park, IL 60085
c Becton-Dickinson, Rutherford, NJ 07070

As cardiology personnel become more aggressive with IV nitroglycerin for treatment of angina pectoris, post-infarction and percutaneous transluminal coronary angioplasty (PCTA), doses of nitroglycerin may increase and this phenomena may become more commonplace.

Careful monitoring of ACT times prior to beginning cardiopulmonary bypass will help prevent unrecognized heparin resistance and consequent clotting in the extracorporeal circuit.

In conclusion, we wish to offer a word of caution when these two drugs are used concurrently.

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Questions from the Audience

Question: Mark Morgan, Spartanburg, SC: What is the concentration in your nitroglycerin?
Response: 50 miligrams in 250 D5W.
Question: Alan Becker, New York: I'd just like to ask if you can speculate maybe or have any ideas as to how this mechanism occurs with the nitroglycerin and heparin, as to what point in the clotting cascade or where or how the nitroglycerin actually affects the heparin?
Response: At this point we don't know. I'll be perfectly honest. There are several possible things we are investigating. I'll list of a few of them:
A complex is formed between plasma protein and nitroglycerin that acts somewhat like protamine. There is an inactivation inhibiting the effect of AT3. There is the possible release of platelet factor 4 which neutralizes heparin. Nitroglycerin may neutralize the negative effect held by heparin. Perhaps a chemical bond is formed among heparin, nitroglycerin and blood elements. I'm sure there are other things to be investigated. These are just some of the preliminary ones that we are looking at. Currently we are using electron capture chromatography to measure the heparin levels in our patients. We are hoping to find what this threshold effect is. At that time maybe we can calculate and say, "Okay, your patient has been on nitroglycerin for this amount of time at this body weight. There you need to give this much nitroglycerin." But at this point we are investigating further but we do not have these answers.