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Effects of Tocainide, an Oral Analogue of Lidocaine, on Thromboembolism after Total Hip Replacement

Jan Modig,[1] Tommy Borg,[1] Göran Karlström,[2] Bo Sahlstedt[3] and Leif Rikner[4]

Departments of Anaesthesiology[1], Orthopaedic Surgery[2] and Diagnostic Radiology[3], University Hospital, Uppsala and Medical Departments, AB Hässle[4], Mölndal, Sweden

ABSTRACT

In an investigation of deep venous thrombosis and pulmonary embolism, where neither dextran nor other antithrombotic drug prophylaxis was employed, 30 patients subjected to total hip replacement under general anaesthesia were randomly allotted to one of two groups. One group (n=15) received tocainide, an oral analogue of lidocaine, as a means of preventing thromboembolism; the other group (n=15) served as a control. In patients given tocainide the frequency of deep venous thrombosis involving the femoral veins, as observed at phlebography, was 60 % (9 of 15), and in the control group 73 % (11 of 15). The frequency of pulmonary embolism, as determined by pulmonary perfusion lung scanning, was 20 % (3 of 15) in the tocainide group and 33 % (5 of 15) in the control group. It was concluded that tocainide administration had no effect as an antithromboembolic agent. Phlebography revealed that the pattern of deep venous thrombosis after total hip replacement was characterized by a high frequency of isolated thigh vein thrombi in the operated leg, probably related to the surgical procedure. A finding of possible clinical significance was that patients given tocainide had a significantly lower intraoperative blood loss than control patients.

INTRODUCTION

Deep venous thrombosis is a common complication following surgical procedures. It appears to occur particularly in patients undergoing major orthopaedic hip surgery, where the incidence has been reported to vary from 20 to 80 % depending on the technique used for diagnosing the thrombosis and the nature of the prophylactic measures (9). Our observations that thigh vein thrombi after total hip replacement were invariably attached to the venous wall of the femoral veins in the region of the surgical area would seem to indicate local endothelial damage with consequent thrombus formation (6). Venous endothelial damage has been shown to be produced by massive adhesion of leukocytes to venular endothelium and transendothelial migration of leukocytes towards a chemotactic center - i.e. the surgical wound (3, 13). Further, it has been found that white-cell-induced endothelial damage can be blocked by lidocaine (3, 13). Thus, Cooke et al. (2) found in 1977 that lidocaine given as an intravenous infusion intraoperatively and for the following six postoperative days in patients subjected to total hip replacement significantly reduced the incidence of deep venous thrombosis as compared with that in a control group given 5 % dextrose. Recently it has been shown that tocainide, a primary amine analogue of lidocaine, also blocks leukocyte locomotion and thus possibly prevents endothelial damage (12).

The aim of the present investigation was therefore to see whether tocainide had the same efficacy as that reported for intravenous lidocaine (2) in the prophylaxis of deep venous thrombosis after total hip replacement. Tocainide would offer significant practical advantages over lidocaine, since it does not undergo rapid hepatic metabolism and could therefore be administered orally. With a biological half-life of about 13.5 h it would be employed in a two or three times a day oral dosage schedule (16).

PATIENTS AND METHODS

Patients

Thirty-three patients suffering from severe osteoarthritis of the hip joint and undergoing total hip replacement entered the study. The patients were randomly allotted, according to their date of birth, to one of two groups, one group of 17 patients who were given tocainide, and a control group of 16 patients. Three patients were later excluded from the study: one patient in the tocainide group because of severe nausea and another owing to technical difficulties with the postoperative phlebographic examination, and one patient in the control group, because of varicose veins. The remaining 30 patients, 15 patients in each group, had no history or symptoms of heart or lung disease, diabetes, previous thromboembolism, varicose veins, or leg ulcers, and all were included in the study.

Investigation scheme

In order to compare the frequency of thromboembolism between the two groups of patients without the influence of factors other than the effect of tocainide administration, all drugs with known antiplatelet activity were withdrawn for 10 days before operation, during operation and for 11 days postoperatively. For the same reason no dextran, heparin or other thromboprophylactic agents were given during this period. Chest radiography combined with perfusion lung scanning was performed three days preoperatively.
Eleven days postoperatively these procedures were repeated, together with bilateral phlebography. Both groups followed the same physiotherapy program, with

early ambulation. The policy has been to permit standing with full weight-bearing on the day after operation.

Administration of trial drug

The patients of the tocainide group took their first dose of tocainide, 400 mg orally, 72 h before surgery, and continued to take this dose 8 hourly before operation and for 11 days postoperatively. Blood samples for determination of the plasma tocainide level were taken immediately before operation, immediately after operation, 3 and 6 h postoperatively and on the 2nd, 4th, 7th and 11th days after operation.

The investigation was approved by the Ethical Committee of the Faculty of Medicine, University of Uppsala. The patients gave their informed consent. No complications occurred in association with the study.

Anaesthesia

In both groups general anaesthesia was induced by a sleep dose of thiopentone and muscular relaxation was achieved with pancuronium bromide. Anaesthesia was maintained with nitrous oxide and intravenously administered fentanyl and pancuronium bromide. Intermittent positive pressure ventilation was delivered via an endotracheal tube. For reversal of neuromuscular block, atropine and prostigmine were given. Naloxone was administered when required to counteract postoperative fentanyl drowsiness.

Operative procedure

All operations were performed with a standardized technique by the same surgeon. The patients lay supine and a lateral incision was made. No trochanteric osteotomy was performed. Acrylic bone cement was used for fixation of the Charnley total hip prostheses. Operative blood loss was estimated by measuring the blood in the suction container and by weighing swabs and drapes. Postoperative blood loss was calculated from suction drainage bottles. Care was taken to replace blood loss by packed red cells, balanced glucose-electrolyte solutions and whole blood intra- and postoperatively. No dextran or other colloidal solution was given.

Phlebography

Bilateral phlebography was carried out 11 days postoperatively. The patient lay supine on a universal X-ray table with a motor-driven table top (Siregraph, Siemens). The table was tilted about 60^{o}. After puncture of a dorsal foot vein, contrast medium (Urografin 45 %; Schering) was injected under fluoroscopic control. Films were exposed over the lower leg in frontal and lateral projections with and without a tourniquet around the ankle. Sometimes a tourniquet was also used above the knee for better contrast filling of the soleal and gastrocnemic veins. The thigh and pelvic veins were examined only in the frontal view. The total amount of contrast medium given averaged about 200 ml. Deep venous thrombosis was diagnosed if a defect appeared on the phlebogram, i.e. (1) a contrast filling defect seen on at least two films or (2) non-visualization of a deep vein combined with collateral circulation. The phlebograms were scrutinized by an experienced radiologist who was unaware of the group to which the patient belonged.

Scintigraphy

Perfusion lung scanning was performed preoperatively and repeated 11 days postoperatively, in an identical manner on the two occasions. Pulmonary perfusion images were obtained with a scintillation camera (Radicamera, General Electric) after intravenous administration of 100 MegaBequerele of ^{99m}Technetium-labelled macroaggregated human serum albumin (Kabi Diagnostica). A low-energy high-resolution parallel-hole collimator was used. Imaging was started immediately after injection. One frontal, one dorsal and one 45^{o} dorsal oblique projection were recorded for each lung. The purpose of the preoperative pulmonary perfusion scanning was to disclose any variations in the pulmonary perfusion pattern and thus reduce the risk of "false positive perfusion defects". Pulmonary embolism was diagnosed if a new defect with a strictly segmental or lobar configuration appeared on the postoperative perfusion lung scan, and if no other cause of the defect could be found at radiography. Minor or atypical perfusion defects on the postoperative pulmonary perfusion scan were not diagnosed as pulmonary embolism.

Plasma tocainide concentrations were determined by high-performance liquid chromatography as described by Lagerström and Persson (5). The determinations were kindly carried out at the Departments of Analytical Chemistry and Biochemistry, AB Hässle, Mölndal, Sweden.

Statistical methods

Student´s t-test was used for comparison of continuous variables. A Chi-square test with Yates´ correction was used for fourfold tables.

RESULTS

The control and tocainide groups did not differ significantly in age, sex distribution, height/weight ratio or duration of anaesthesia or operation. In this series of patients it was a constant aim to replace both intraoperative and postoperative blood losses immediately and completely by electrolyte-glucose solutions, packed red cells and whole blood in order to avoid reductions in the circulating blood volume. Intraoperative blood loss and intraoperative transfusion requirements were significantly smaller in patients given tocainide. There were no differences in hematocrit values either when measured immediately postoperatively or later in the postoperative course.

The study was stopped after 30 patients (15 patients in each group), because of the high incidence of deep venous thrombosis and pulmonary embolism. A sensitive phlebographic technique was employed and all thrombi detected, no matter how small, were recorded as deep venous thrombosis. The frequency of deep venous thrombosis involving both the calf and thigh veins was 73 % in the control group, and 60 % in patients given tocainide.

The site, extension and distribution of deep venous thrombosis are illustrated schematically for both groups of patients in Figs 1 and 2, which also present the patients who developed pulmonary embolism.

One interesting observation is that thigh vein thrombi had formed as separated entities in the operated leg. Only one of 20 thigh vein thrombi was in continuity with a thrombus in a calf vein. Furthermore, patients developing pulmonary embolism always had phlebographic signs of deep venous thrombosis involving the femoral veins. In five patients in the control group pulmonary embolism was diagnosed on the postoperative perfusion lung scan. Three of them had clinical symptoms of this condition, such as chest pain and cough. Three patients in the tocainide group had pulmonary embolism and in one of them this gave rise to symptoms. Thus, no significant differences were observed between the control and tocainide groups in either the frequency of deep venous thrombosis involving the calf or thigh veins, or the frequency of pulmonary embolism.

Plasma levels of tocainide are given in Table 5. All values were within the therapeutic range for an antiarrhytmic effect (4).

Adverse reactions such as nausea and skin rash occurred in four patients of the tocainide group. In one of these patients the trial had to be terminated because of severe nausea. This patient was therefore excluded from the study.

Table 1. Distribution of the two groups of patients by sex, age, height/weight ratio, duration of anaesthesia and duration of operation. Mean values and standard deviations are given.

	n	Female/Male	Age (years)	Height/Weight ratio	Duration of anaesthesia (min)	Duration of operation (min)
Control	15	7/8	65.9±6.2	2.17±0.22	221±36	157±33
Tocainide	15	5/10	62.2±8.6	2.23±0.31	208±38	141±40

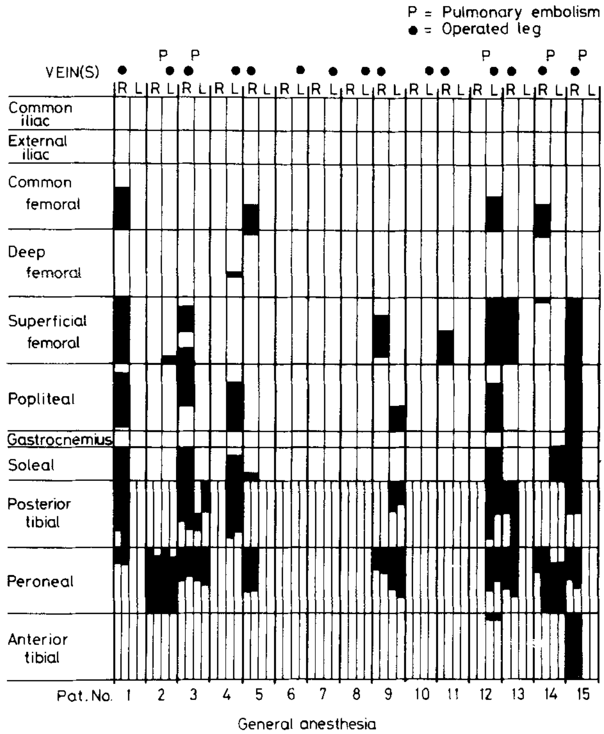

Fig. 1

Schematic representation of site, extension and distribution of deep venous thrombosis and of pulmonary embolism in control patients.
● = Site of operation, right or left leg.
P = Pulmonary embolism.

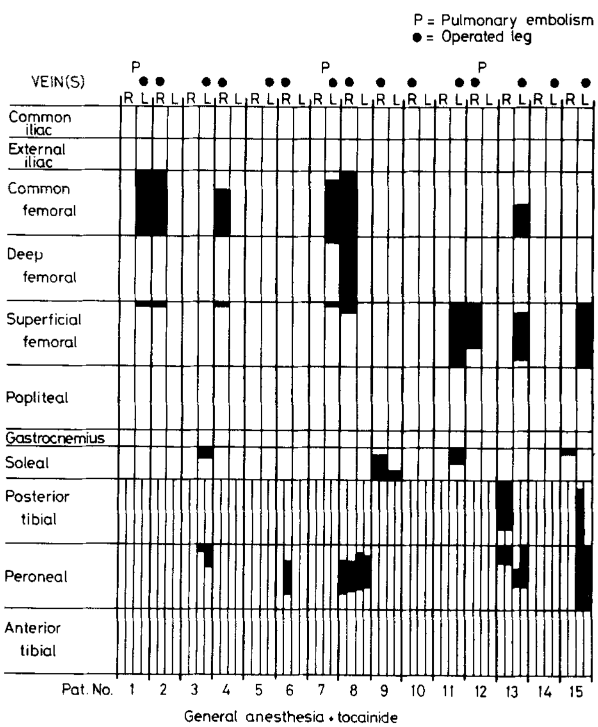

Fig. 2

Schematic representation of site, extension and distribution of deep venous thrombosis and of pulmonary embolism in patients receiving tocainide.
● = Site of operation, right or left leg.
P = Pulmonary embolism.

Table 2. Intraoperative blood loss as estimated by measurement of blood in the suction container and weighing of swabs and drapes, intraoperative blood transfusion and postoperative hematocrit in the two groups of patients. Mean values and standard deviations are given.

	Intraoperative blood loss (ml)	Intraoperative blood transfusion (ml)	EVF immediately postoperatively	EVF 2nd postoperative day
Control	1737±456	1760±422	38.3±2.9	36.2±3.0
Tocainide	1293±315 $p < 0.01$	1300±304 $p < 0.01$	38.2±3.5	36.1±3.2

Table 3. Phlebographic findings

	Normal	Isolated calf vein thrombosis	Calf and thigh vein thrombosis	Thigh vein thrombosis without calf vein thrombosis
Control	4	0	10	1
Tocainide	3	3	4	5

Table 4. Perfusion lung scan findings

	Normal	Segmental perfusion defect(s) (Pulmonary embolism	Minor or atypical perfusion defects
Control	7	5	3
Tocainide	10	3	2

Table 5. Tocainide concentrations, µmol/l

	Day 0							
	Immediately before op	Immediately after op	3 h postop	6 h postop	2 days postop	4 days postop	7 days postop	11 days postop
Mean	22.8	31.1	33.5	27.9	29.8	30.3	27.1	25.3
SD	6.5	7.3	7.6	5.4	7.0	8.5	8.6	6.8
n	14	14	15	14	14	14	11	13

DISCUSSION

In this investigation deep venous thrombosis was diagnosed by phlebography. All deep veins, including the muscle veins of the calf, were included and the deep veins were examined up to the confluence with the inferior vena cava. All thrombi detected, no matter how small, were recorded as deep venous thrombosis, which might be one explanation for the high frequency of this condition. The exclusion of both colloidal and pharmacological thromboprophylactic agents in this series of patients would be another contributory factor.

The perfusion lung scan is very sensitive, false negative results being extremely rare (14, 15). False positive results are common and any observed perfusion defects should be compared with the findings in the chest X-ray, as conditions other than pulmonary emboli, such as pneumonia, atelectases and pleural effusions can give rise to perfusion defects (10). The specificity of the perfusion scan can be improved by accepting only segmental or lobar defects as diagnostic of pulmonary embolism, and only if no other cause of this defect can be found at chest X-ray. In the present patients minor or atypical perfusion defects could be explained by pathological findings of the radiograph.

In this series of randomized patients, tocainide, an oral analogue of lidocaine, had no beneficial effect in preventing deep venous thrombosis or pulmonary embolism after total hip replacement. This is contrary to the results with lidocaine found by Cooke et al. (2). It seems therefore that factors other than leukocyte adhesion and transendothelial migration with consequent endothelial damage in the operated leg - as suggested by Cooke et al. (2) - were responsible for the formation of deep venous thrombi in our patients. From this study, it can moreover be concluded, that deep venous thrombosis after total hip replacement is of two main types: 1) Thrombosis in the lower leg, probably caused by stasis and general effects of trauma, and 2) thrombosis caused by local factors involving the thigh veins on the side of surgery. It is very unlikely that local anaesthetics have any effect in counteracting a retarded blood flow (8) or general effects of trauma such as an increased tendency to clotting and impaired fibrinolytic function (7). Furthermore, in the light of the recent findings by Stamatakis et al. (11), it also seems very unlikely that local anaesthetics are able to influence the endothelial damage caused by the operative procedure. These authors found, with the aid of intraoperative phlebography, that severe distortions of the femoral veins occur as a result of manipulation of the operative leg during surgery. This probably causes endothelial damage and thereby initiates thrombus formation, and could explain the high incidence of deep venous thrombosis in the thigh on the operated side in the present investigation.

Finally, a finding of both statistical and possible clinical significance was the lower intraoperative blood loss in patients given tocainide. It has been shown (1) that local anaesthetics of the amide type increase the vascular tone and thereby reduce the blood flow to the operation wound. Though this finding could be due to an effect of tocainide on peripheral vascular resistance, there were no significant changes in blood pressure between the two groups noted either during or after the operation. Furthermore, the tocainide treated patients were, on average, younger, less obese and had shorter duration of operation, all of which should contribute to reduced blood loss. In view of these observations the exact role of tocainide in the reduction of intraoperative blood loss remains speculative.

To conclude:

The pattern of deep venous thrombosis following total hip replacement is characterized by a high frequency of isolated thigh vein thrombi in the operated leg, probably related to the surgical manipulation. Administration of tocainide, an oral analogue of lidocaine, has no effect in reducing the frequency of deep venous thrombosis. However, tocainide administration was associated with a significantly reduced intraoperative blood loss, which saves donor blood.

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Address for reprints:

Jan Modig, M.D.
Department of Anaesthesiology
University Hospital
S-750 14 UPPSALA
Sweden