ORIGINAL INVESTIGATION

Relationship of Serotonergic Antidepressants and Need for Blood Transfusion in Orthopedic Surgical Patients

Kris L. L. Movig, PhD; Michiel W. H. E. Janssen, MD; Jan de Waal Malefijt, MD, PhD; Peter J. Kabel, MD, PhD; Hubert G. M. Leufkens, PhD; Antoine C. G. Egberts, PhD

Background: Several reports of various bleeding problems associated with the use of serotonergic antidepressants have been published. However, no information concerning the effect of these drugs on perioperative blood loss and blood transfusion requirements during orthopedic surgery is available. The objective of this study was to determine the association between use of serotonergic antidepressants and perioperative blood loss and transfusion in orthopedic surgical patients.

Methods: A retrospective follow-up study, using routinely collected hospital and pharmacy data, was conducted among all orthopedic patients undergoing surgery from January 1, 1999, through December 31, 2000. The actual blood transfusion requirements and blood loss during surgery were assessed. Patients were divided into 3 groups for comparison: users of serotonergic antidepressants, users of nonserotonergic antidepressants, and nonusers of antidepressants. The Medical Ethics Committee approved the study protocol, and informed consent was obtained from all patients or their legal relatives.

Results: A total of 520 subjects with evaluable data participated in the study. The risk of blood transfusion almost quadrupled for the serotonergic antidepressant group as compared with the nonusers (adjusted odds ratio, 3.71; 95% confidence interval, 1.35-10.18). Patients using nonserotonergic antidepressants had no increased risk (odds ratio, 0.74; 95% confidence interval, 0.10-5.95).

Conclusions: Use of serotonergic antidepressants is associated with an increased risk of bleeding and subsequent need for blood transfusion during orthopedic surgery. The bleeding could be attributed to inhibition of serotonin-mediated platelet activation.

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From the Hospital Pharmacy Midden-Brabant, St Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands (Drs Movig and Egberts); Departments of Orthopaedic Surgery (Drs Janssen and de Waal Malefijt) and Medical Microbiology (Dr Kabel), St Elisabeth Hospital, Tilburg; and Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands (Drs Movig, Leufkens, and Egberts). *The authors have no relevant financial interest in this article.*

SELECTIVE SEROTONIN reuptake inhibitors, first introduced in the late 1980s, have become one of the most widely prescribed classes of drugs. They are frequently used in elderly patients to treat psychiatric diseases, such as depression and obsessive-compulsive disorders.[1] It has been suggested that selective serotonin reuptake inhibitors have lower incidence and severity of side effects than the older antidepressants, such as monoamine oxidase inhibitors and tricyclics.[2]

Several reports have shown that the use of antidepressants, tricyclics as well as selective serotonin reuptake inhibitors, increases the risk of falls and related bone fractures among elderly people.[3,4] The reasons for this increased risk are complex and may include sedation, orthostatic hypotension, and confusion.[5] Of the patients who experience fractures while using antidepressants, many require joint arthroplastic surgery. There is as yet no information available concerning the effect of serotonergic antidepressants on perioperative blood loss, or the requirements for blood transfusion in orthopedic patients. Perioperative blood transfusion increases the risk of postoperative infections and mortality.[6] In the past few years, however, there has been an increase in the number of case reports[7-21] and studies[22-26] describing bleeding disorders (especially gastrointestinal) associated with the use of serotonergic antidepressants. These reports have raised concerns regarding the safety of serotonergic antidepressants in elderly patients undergoing orthopedic surgery. The objective of this study was to investigate the relationship between the serotonergic antidepressants and the need for blood transfusion during orthopedic surgery.

METHODS

SETTING

The study was conducted in a large general teaching hospital (St Elisabeth Hospital) in Til-

burg, the Netherlands. The study population consisted of all patients who received hip, knee, or spine implants during the period from January 1, 1999, through December 31, 2000. Patients were identified by means of a computerized database that contains information on all orthopedic operations performed within the study period. In the Tilburg region, all blood transfusion requirements and biochemical laboratory data from inpatients and outpatients are compiled into one database. The Medical Ethics Committee approved our study protocol, and we obtained informed consent for the use of medical records from all patients or their legal relatives.

DESIGN

We investigated the risk of perioperative blood transfusion, in particular related to serotonergic antidepressants, in a group of orthopedic surgical patients in a nonconcurrent cohort study. Patients were excluded from the study if (1) no informed consent was obtained, (2) medical records were missing, and (3) drug prescription data were incomplete. The need for blood transfusion during surgery was used as a primary outcome variable. Furthermore, for all included patients, bleeding during operation, infusion requirements, and loss of drainage fluid were also noted. Drug prescription data for all hospitalized patients were obtained from community pharmacies. A strong pharmacy-patient liaison in the Netherlands ensures that the majority of patients are registered with the same pharmacy for the dispensing of their prescription drugs, guaranteeing optimal recording of drug use patterns.[27] Data on morbidity and comorbidity and perioperative and postoperative information were obtained from medical records.

For the present study, we categorized antidepressants into 2 groups on the basis of their inhibitory properties of serotonin reuptake rather than chemical structure.[28] The first group, serotonergic antidepressants, consisted of antidepressants, such as clomipramine hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine, sertraline hydrochloride, and venlafaxine hydrochloride, that act mainly on the serotonergic system. Clomipramine and venlafaxine were included in the first group because both are known to be potent antagonists of the serotonin reuptake mechanism.[28] The second group consisted of nonselective serotonergic-acting antidepressants.

The following covariates were studied as possible confounding factors: current use of aspirin, calcium-channel blockers, corticosteroids, iron supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), vitamin K antagonists, and methotrexate. The confounding effects of concomitant diseases, such as diabetes mellitus, heart failure, hypertension, hepatic and renal diseases, and bleeding ulcers, were also considered.

DATA ANALYSIS

The association between exposure to serotonergic antidepressants compared with no exposure to any antidepressant and the need for blood transfusion was evaluated by means of logistic regression analysis. Patients who were given blood transfusion were compared with those who did not require a transfusion by means of logistic regression analysis. Odds ratios and 95% confidence intervals were estimated. The final model included age and sex and all univariate (P.10) associated risk factors.

Measurements of hemostasis, including perioperative blood loss, fluid infusion, and postoperative drainage, were determined for the serotonergic and nonserotonergic antidepressant groups. An analysis of variance with paired, 2-tailed t test was performed to assess the significance of differences in the mean of continuous variables between patient groups. Differences in proportions of categorical variables were tested for significance by a χ^2 test. All statistical calculations were carried out with the SPSS statistical package (version 10.0; SPSS Inc, Chicago, Ill).

Table 1. General Characteristics of All Study Patients, Including Subgroups of Patients Requiring and Not Requiring Blood Transfusion During Surgery

	All Patients (n = 520)	Blood Transfusion (n = 59)	No Blood Transfusion (n = 461)
Demographic characteristics			
Age, y			
Mean (SD)	68 (12)	66 (11)	68 (12)
No. (%)			
<65	182 (35)	21 (36)	161 (35)
≥65	338 (65)	38 (64)	300 (65)
Sex, No. (%)			
Male	154 (30)	20 (34)	134 (29)
Female	366 (70)	39 (66)	327 (71)
Preoperative hemoglobin, mean (SD), g/dL	11.12 (1.66)	10.51 (1.47)	11.33 (1.68)
Type of implant, No. (%)			
Hip	361 (69)	47 (80)	314 (68)
Knee	130 (25)	8 (13)	122 (27)
Spine	29 (6)	4 (7)	25 (5)
Anesthesia, No. (%)			
General	375 (72)	42 (71)	323 (72)
Spinal	145 (28)	17 (29)	128 (28)
Medication, No. (%)			
Aspirin	64 (12)	6 (10)	58 (13)
Antidepressants	40 (8)	7 (12)	33 (7)
Serotonergic	26 (5)	6 (10)	20 (4)
Nonserotonergic	14 (3)	1 (2)	13 (3)
Calcium channel blockers	51 (10)	6 (10)	45 (10)
Corticosteroids	19 (4)	1 (2)	18 (4)
Iron supplements	19 (4)	4 (7)	15 (3)
Methotrexate	16 (3)	4 (7)	12 (3)
Neuroleptics	27 (5)	3 (5)	24 (5)
NSAIDs	191 (37)	28 (47)	163 (35)
Vitamin K antagonists	9 (2)	1 (2)	8 (2)
Morbidity and comorbidity, No. (%)			
Diabetes mellitus	48 (9)	5 (8)	43 (9)
Heart failure	15 (3)	2 (3)	13 (3)
Hypertension	139 (27)	17 (29)	122 (26)
Renal disease	8 (2)	0	8 (2)
History of bleeding ulcers	6 (13)	0	6 (13)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.
SI conversion factor: To convert hemoglobin to millimoles per liter, multiply by 0.6206.

RESULTS

A total of 520 patients were included in the study. Although 685 suitable orthopedic procedures, corresponding to 643 patients, were recorded during the study period, lack of informed consent (16 patients) and missing (22) or incomplete (127) medical files were major reasons for exclusion (some patients had more than 1 reason for exclusion). There were no clinically important differences between included and excluded patients.

Table 1 summarizes the main baseline characteristics of all study patients. Female patients constituted 70% of the study population, and the mean age was 68 years. Fifty-nine patients (11%) required perioperative transfusion. The mean blood loss and fluid infusion volume during surgery were 1277 mL and 3016 mL, respec-

Table 2. Comparison of Hematologic Measures of Patients Using a Serotonergic Antidepressant and All Other Patients Not Using a Serotonergic Antidepressant

	Serotonergic Antidepressants (n = 26)	Nonserotonergic Antidepressants (n = 494)	*P* Value
Blood transfusion, No. (%)	6 (23)	20 (4)	<.001
Preoperative hemoglobin, mean (SD), g/dL	10.52 (1.16)	10.62 (1.24)	.72
Perioperative blood loss, mean (range), mL	1019 (0-8500)	582 (0-7500)	.001
Perioperative fluid infusion, mean (range), mL	2434 (300-5000)	2458 (200-9500)	.37
Postoperative drainage, mean (range), mL	657 (60-1750)	495 (0-3000)	.03

SI conversion factor: To convert hemoglobin to millimoles per liter, multiply by 0.6206.

Table 3. Crude and Adjusted Odds Ratios for Blood Transfusion According to Age, Sex, Comedication, and Comorbidity

	OR (95% CI)	
Risk Factor	Crude	Adjusted*
Age ≥65 y	0.97 (0.55-1.71)	1.22 (0.67-2.20)
Female sex	0.80 (0.45-1.42)	0.82 (0.45-1.53)
Comedications		
Aspirin	0.79 (0.32-1.91)	0.82 (0.32-2.06)
Antidepressants		
None	Reference	Reference
Serotonergic	2.47 (0.95-6.43)	3.71 (1.35-10.18)
Nonserotonergic	0.63 (0.08-4.94)	0.74 (0.10-5.95)
Calcium channel blockers	1.05 (0.43-2.57)	1.04 (0.41-2.63)
Corticosteroids	0.43 (0.06-3.24)	0.30 (0.04-2.43)
Iron supplements	2.16 (0.69-6.75)	2.00 (0.51-7.85)
Methotrexate	2.72 (0.85-8.73)	2.54 (0.79-9.64)
Neuroleptics	0.98 (0.29-3.34)	1.02 (0.29-3.66)
NSAIDs	1.65 (0.96-2.85)	1.66 (0.92-2.98)
Vitamin K antagonists	0.98 (0.12-7.95)	1.14 (0.14-9.54)
Morbidity and comorbidity		
Diabetes mellitus	0.90 (0.34-2.37)	1.03 (0.38-2.81)
Heart failure	1.21 (0.27-5.50)	1.18 (0.24-5.74)
Hypertension	1.13 (0.62-2.05)	1.26 (0.68-2.35)

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.
*Adjusted for age, sex, antidepressants, methotrexate, NSAID, and type of operation.

tively, for patients who received transfusions as compared with 445 mL and 2309 mL for patients who did not receive transfusions. An average of 2.0 U (range, 1-6 U) of packed red blood cells was given to patients who required a transfusion. We found a significant association between the need for perioperative transfusion and the preoperative hemoglobin level (P=.007).

Overall, 26 patients (5%) used serotonergic antidepressants before surgery: paroxetine (14 patients), fluoxetine (4), clomipramine (4), venlafaxine (2), fluvoxamine (1), and sertraline (1). Of these patients, 6 (23%) received perioperative blood transfusions (**Table 2**). Use of these antidepressants was significantly associated with increased blood loss during surgery (1019 mL for users vs 582 mL for nonusers; P=.001). Although the perioperative fluid requirements appeared to be unaffected, the postoperative drainage was slightly higher in the antidepressant group.

The risk of blood transfusion almost quadrupled for the serotonergic antidepressant group as compared with the nonusers (adjusted odds ratio, 3.71; 95% confidence interval, 1.35-10.18) (**Table 3**). The use of comedications, NSAIDs, methotrexate, or iron supplements also increased the risk of perioperative blood transfusion. This increased risk was not found, however, for patients using nonserotonergic antidepressants, vitamin K antagonists, calcium-channel blockers, or corticosteroid treatment.

COMMENT

We found an association between serotonergic antidepressants and the need for blood transfusion among orthopedic surgical patients. In the present study, patients using serotonergic agents lost significantly more blood during orthopedic surgery than those not using any antidepressant. Evidence from case reports has indicated a possible link between serotonergic antidepressants and bleeding-related problems.[7-21] Other studies have demonstrated that serotonergic antidepressants are associated with a substantially greater risk of major gastrointestinal bleeding,[22] particularly in patients concomitantly taking NSAIDs.[25] Recently, de Abajo et al[25] reported a 3-fold increase in the risk of gastrointestinal bleeding in adult primary care patients. A large incidence study estimated an absolute risk of serotonergic antidepressant–induced gastrointestinal hemorrhages of 8 new hemorrhages per 1000 persons treated per year in elderly patients (65 years and older).[22] There was no increased risk of intracranial bleeding among serotonergic antidepressant users.[24]

The main pharmacologic mechanism for the increased risk in prolonged bleeding may occur via a decrease in intraplatelet serotonin concentrations affecting platelet aggregation.[29] Furthermore, decreased platelet serotonin and a concurrent increase in plasma serotonin levels have also been associated with surgical procedures.[30] Thus, patients experiencing stress from surgical procedure are thought to be at higher risk for bleeding complications because of platelet impairment. The combination of these 2 effects may act synergistically to negatively influence hemostasis, resulting in an even higher bleeding risk. In this context, serotonergic antidepressants have recently been associated with decreased cardiovascular diseases, suggesting a thrombolytic mechanism of action.[31]

Aspirin and other NSAIDs cause prolonged bleeding by inhibiting prostaglandin endoperoxides and thromboxane A_2 in platelets. The NSAIDs are widely used for painful osteoarthritis in orthopedic and rheumatology patients who subsequently require joint arthroplasty surgery. Robinson et al[32] found that the risk of perioperative blood loss associated with NSAIDs doubled among patients undergoing total hip arthroplasty. Increased postoperative blood loss was also associated with NSAID

use.[33,34] Our present findings concerning NSAIDs concur with these studies. The use of calcium-channel blockers has been associated with a 2-fold increased risk of perioperative bleeding in hip surgical patients.[35] In the present study, no elevated risk of perioperative blood transfusion was found for patients using calcium-channel blockers; they, however, experienced an increased need for postoperative blood transfusion requirements (data not shown). Ambulatory patients using intramuscular methotrexate are usually treated for rheumatoid arthritis. Although methotrexate itself is not known to be associated with an increased risk of bleeding, our finding confirms the findings of an earlier study of the need for perioperative blood transfusion in orthopedic patients with rheumatoid arthritis.[36]

As with other observational studies, our study may have been affected by bias and confounding, related to the effects of factors (other than the exposure of interest) on the risk of the outcome. However, we believe it is unlikely that any potential biases have significantly affected our results. First, information bias seems highly unlikely because bleeding complications during orthopedic procedures are not, in daily clinical practice, generally associated with serotonergic antidepressants. Serotonergic antidepressants are not mentioned in the orthopedic protocol as potentially dangerous for bleeding complication, unlike the recommendation for aspirin to be stopped 1 week before surgery. Thus, as expected, no association between this agent and the outcome in this study has been found. Referral bias is highly unlikely because of the seriousness of the orthopedic procedures and clinical events in question.

Second, since all patients were sampled from a well-defined population, we believe that selection bias was not an important issue in this study. Because of the study's retrospective design, all information had been collected in the past; thus, recall bias is negligible. Data needed for endpoint definition were electronically obtained from the hematological laboratory, which has highly secured procedures controlling and documenting blood transfusion requirements in our clinic. The medical record review was performed blinded to drug exposure. Prescription data from Dutch community pharmacies are virtually complete and have high agreement with the patients' adherence, so misclassification of antidepressant, or other drug, use is unlikely. If so, any selection bias or misclassification would have been nondifferential, underestimating the risks.

Although we controlled for several factors, confounding by indication cannot be excluded. There is evidence that depression itself might be associated with alterations in platelet serotonin levels, which may be further influenced by antidepressant treatment.[37,38] In that case, depression itself may increase the bleeding risk.

The introduction of recombinant human erythropoietin into clinical orthopedic practice could decrease the allogeneic blood transfusion requirement, thus avoiding or minimizing transfusion-related complications.[39] However, recombinant human erythropoietin was not used in orthopedic patients routinely in our hospital during the study period.

The present study provides new information. The association between serotonergic antidepressants and perioperative blood transfusion in orthopedic surgery could pose a potential health problem for elderly patients because of the widespread and increasing use of antidepressants. A relatively large number of patients may be exposed to this potential risk. Although increased bleeding is clinically important and should be considered for orthopedic patients using serotonergic antidepressants, it remains an uncommon adverse effect that should carefully be examined along with other information.

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Corresponding author: Antoine C. G. Egberts, PhD, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, PO Box 80082, 3508 TB Utrecht, the Netherlands (e-mail: A.C.G.Egberts@pharm.uu.nl).

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