Hematology-2013

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Antipsychotics & venous thromboembolism disease: the great unknow

International Conference on Hematology & Blood Disorders

Track 9: thrombosis & haemostasia

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Introduction

- Psychiatric disease & VTD
- Antipsychotics & VTD
  - Physiopathology
- Antipsychotics & dairy practice
  - Thromboprophylaxis in psychiatric patients
- RIETE data
- Summary

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Psychiatric disease

& VTD

Psychiatric disease & VTD

- Psychiatric illness and VTD
  - In acute phase have a 2.7% incidence of VTD
  - 26% of our patients with VTD have a psychiatric disorder:
    - 5% schizophrenia
    - 28% depression
    - 18% cognitive disorder
  - 2-3 fold higher mortality in general
    - 60% of the causes are somatic: increased cardiovascular morbidity and mortality
  - Not included in clinical trials
  - Schizophrenia and bipolar disorder.
  - Depression
  - Dementia: antipsychotics

- VTD risk factors in psychiatric patients
  - Acute psychosis outbreak as prothrombotic state *per se* elevated markers of inflammation in untreated patients
  - Traditional cardiovascular risk factors
  - Somatic hospitalization: activation of the sympathetic system with elevated catecholamine
  - Prolonged hospitalization and bedrest
    - venous stasis - containment: endothelial damage.
  - Antipsychotics

Masopust J BMC psychiatrics 2011

Jönsson AK CNC Drugs 2012

Marchena et al. SEMI 2011

Masopust J. Psy Clin Neurosci 2012

Psychiatric disease & VTD

- Acute psychosis is a prothrombotic state *per se* elevated markers of inflammation in untreated patients
  - D-dimer , Factor VIII, sP-selectin

Marcador	Patients without antipsychotic	Healthy controls	p
D-dimer	1.12 ± 2.4 mgr /l	0.28±0.3 mgr/l	0.003
Factor VIII	160 ± 72.5 %	123 ± 62.5 %	0.06
sP-Selectins	209 ± 124 ngr /ml	124.1 ± 32 ngr /ml	0.0005

- Raised levels are maintained beyond one year

Masopust J et al. BMC Psychiatry 2011

Psychiatric disease & VTD

- USA : hospitalized patients
  - 28723771 hospitalized 2006
  - 450951 (1.6%) consume antipsychotics

	General population	Antipsychotics consumers
PEs cases	76814 (0.3%)	3764 (0.83%)

  - OR variable unadjusted : 3.25 (3.14-3.68) p < 0.001
  - OR variable adjusted : 1.17 (1.13-1.21) p < 0.001

Allenet B. Pharmacoepidemiol Drug Saf. 2012

Antipsychotics

& VTD

Antipsychotic

- Casos registrados de asociación con ETEV desde 1950
- 2000
  - Alerta clozapina por 5 casos fatales
- 2008
  - OMS: efecto secundario
- Estudios observacionales y casos-controles

Hägg. S. Lancet 2000

Hägg. S. Drug Saf 2008

Antipsychotic

- 1.5-5 fold higher risk than non consumer
- Second generation & first generation low power
  - Meta-analysis: 7 cases and controls (31095 cases vs 143472 controls)

Antipsychotics	OR	IC 95%
General	2.39	1.71-3.35
First generation low power	2.91	1.81-4.71
Second generation	2.20	1.22-3.95
First generation high power	1.58	1.50-1.67

Jönsson A. Clinical Epidemiology 2009

Zhang R. Pharmacopsychiatry 2011

Antipsychotic

First Generation	Second Generation
Clorpromazine	Clozapine
Haloperidol	Olanzapine
Flupentixol	Risperidone
Sulpiride	Zuclopentixol
	Quetiapine

- Mediated risk by :
  - Kind of antipsychotic
  - Maximun doses: 2.5-fold higher risk
  - Parenteral way administration : 3 –fold higher risk vs oral intake
  - Firsts three months of treatment
  - Number of antipsychotics: 2.5- fold higher risk mortality per antipsychotic
  - Additive effect with other risk factors: contraceptives

Jönsson A. CNC Drugs 2012

Masopust J Psy Clin Neurosci 2012

Allenet B. Pharmacoepidemiol Drug Saf. 2012

Parker C. BMJ 2010

Antipsychotic

- Prothrombotic mechanisms due to antipsychotics
  - Platelets hyperaggregation
  - Hyperprolactinemia
  - Presence of antiphospholipid
  - Hyperhomocysteinemia
  - Increased immobility by sedation or mechanical clamps: venous stasis

Del Conde , Goldhaber Thromb Haemost 2006

Khammassi , N Encephale 2012

Masopoust Psy Clin Neurosci 2012

Antipsychotic

Hyperaggregation platelet & hyperprolactinemia

- Antipsychotics are dopamine antagonists: increased prolactin
- Prolactin is a physiological cofactor of the coagulation balance in scenarios that increase (pregnancy, antipsychotics, pituitary tumors) and may explain the increased risk of VTE
- Hyperprolactinemia by blocking dopamine receptors D2 pituitary cells contributes to platelet aggregation
- Platelet stimulation is significantly higher in patients with hyperprolactinemia. Prolactin levels correlate the expression of sP-selectin, a marker of platelet activation
- Serotonin platelet amplifier
- Interaction with serotonin receptors that are to modulate the dopaminergic system
- Classic atherosclerotic risk factors

Del Conde. Thromb Haemost 2006

Khammassi N. Tun Med. 2012.

Wallaschofski H et al J. Clin. Psychofarmacol. 2003.

Antipsychotic

Antiphospholipid antibodies

- Antiphospholipid antibodies in schizophrenic patients:
  - Incidence 30% : Ig–M ACA
- Antipsychotics induced Ig-G ACA
  - Clozapine

	SQZ without treatment	SQZ with clozapine	Healthy controls	p
Ig-G ACA (UI)	1.51 ± 0.81	1.72± 0.90	1.25 ± 0.13	0.01
Ig-M ACA (UI)	1.53 ± 0.54	1.62 ± 0.83	1.33 ± 0.14	0.01
r Pearson		0.461		0.01

Schwartz M. J Clin Psychiatry 1998 ; Shen H. J Psychiatric Research 2009

Antipsychotic

Hyperhomocisteinemia

- Schizofrenic patients have raised levels of Hcy:
  - *per se* due to decreased levels of folate with normal B12.
  - High doses of antipsychotics decreased levels of folate.

- Hcy > 20 µmol/L: 34-fold higher risk

	SQZ	Healthy controls	p
Homocysteine	16.1 µmol/L	10.9 µmol/L	0.028
Hyperhomocisteina (> 15 µmol/L)	34%	15.2%	
Folate	4.2 µg/L	8.2 µg/L	0.001

Mabrouk H . Encefale 2011

Eren E. Clin Lab 2010

Rajnic M. Pharmacogenomics 2012

Clinical implication of antipsychotics in VTD

Clinical implication of antipsychotics

- Thromboprophylaxis ?:
  - Prevention of the first episode of VTE
    - Not routinely indicated in acute psychosis income except immobilization
    - General rules if medical or surgical process
  - Recurrence of VTE
    - General rules recurrence risk
  - Not recommended in ambulatory patients with antipsychotics
- Thrombophilia screening ?
  - Not efective
  - General rules as general population
- Retired antipsychotic ?
  - Not routinely
  - Change by other of less thrombotic power.
- How to treat ?
  - According to current recommendation.

Masopust J, Psychiatry Clin Neurosci. 2012

Malý R. Psychiatry Clin Neurosci 2008

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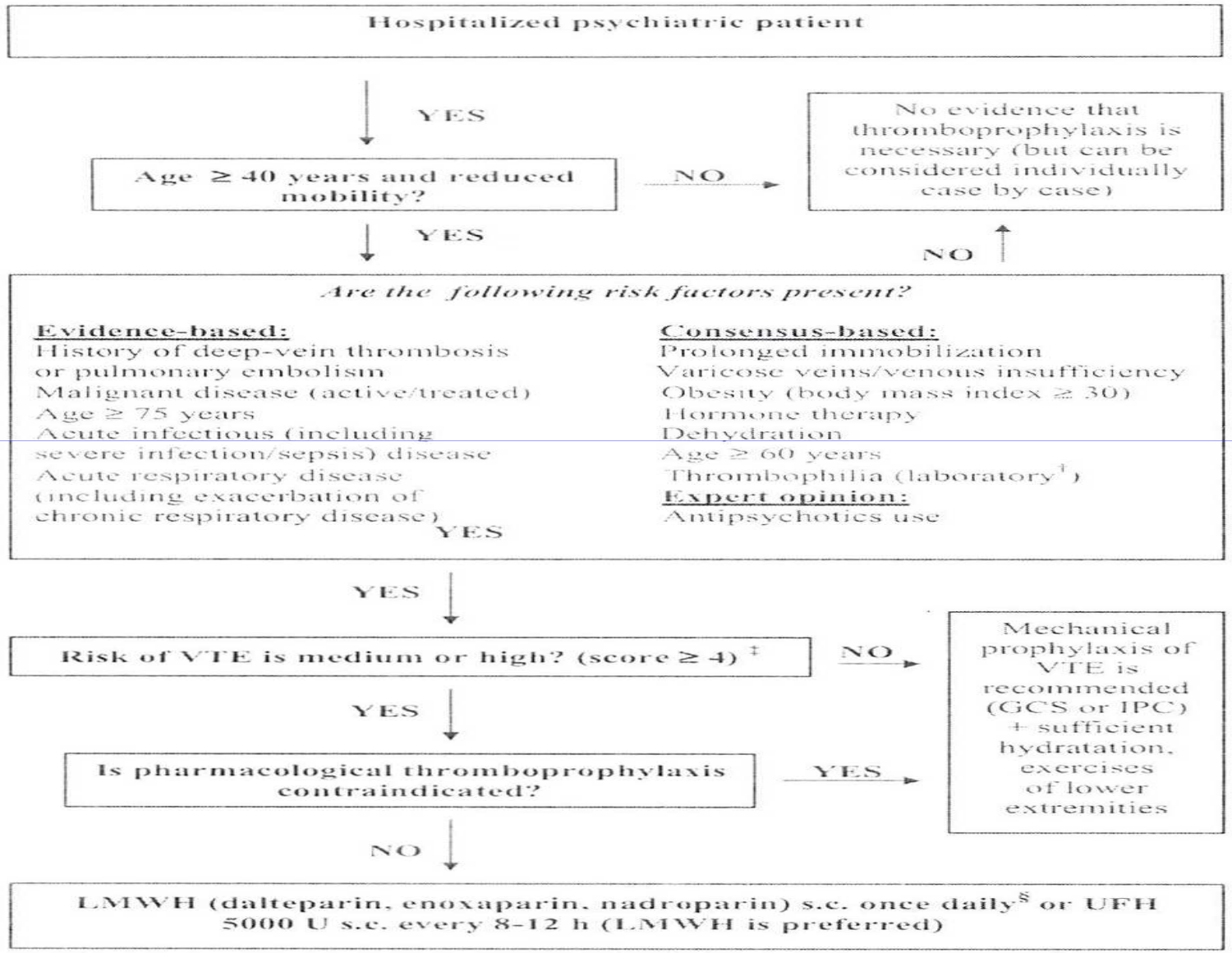
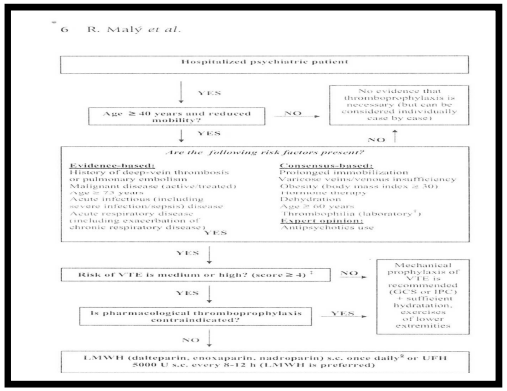
Malý et al.

Malý R. Psychiatry Clin Neurosci 2008



Thromboprophylaxis guide in psychiatrics

hospitalized patients with reduced mobility



Malý R. Psychiatry Clin Neurosci 2008

Risk factors : 2 points	Risk factors : 1 points
Previous VTD	Inmobilization (paralysis containment> 8 hours, catatonia)
Cancer	Estrogenic theraphy
Age > 75	Obesity (IMC > 30)
Acute infection	Age 60-74 años
	Varicose veins / venous insufficiency
	Dehydration
	Thrombophilia
	Antipsychotics

Low risk ≤ 3 points	High risk ≥ 4 points
No pharmacological thromboprophylaxis	LMWH qd sc
Hydration- elastocompression- mechanical devices	

Masopust J, Psychiatry Clin Neurosci. 2012

THROMBOPROPHYLAXIS OF VENOUS THROMBOEMBOLIC DISEASE IN ACUTE MENTAL DISORDERS

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- ***Objective:***
  - To asses the level of fulfillment of thromboprophylaxis in acute psychiatric disorders admitted in our psychiatric acute unit, analyzed the risk factors and the better way to improve.

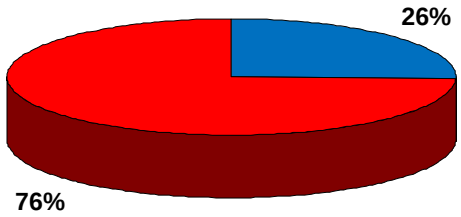
- **Methods:**
  - Descriptive, observational and transversal study carry on one weekday of may 2012 in Acute Psychiatric Unit of our hospital. We analyzed all patients admitted that day and review intake of antipsychotics, intake of chronic anticoagulants and acute mental disorder and the level of fulfillment of thromboprophylaxis according to algorithm of Malý et al 2008

Results

N = 61 patients	Results
Sex (women)	52.5%
Age	44.26 ± 15.21
Previous VTD	4.9%
Current anticoagulation	1.6%
Current antipsychotic	88.5%
Atypical antipsycotic	52%
More than one antipsychotic	50.8%
Antidepressant	36.1%
Inmovilization > 4 days	8.2%
Indication thromboprophylaxis	26.2%
Made thromboprophylaxis	37%

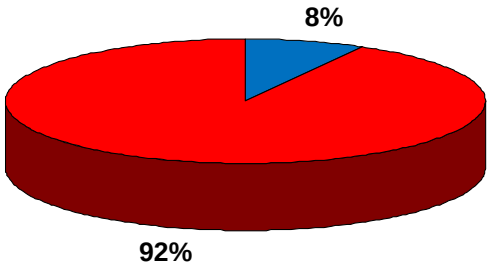
Indicated thromboprophylaxis

p= 0.0001



Tbpx \ Indicate	Yes	No
Yes	37.5%	4.5%
No	56.25%	95%

Thromboprophylaxis and immobilization



Inmovilization \ Indication tbpx	Yes	No
Yes	31.25%	0
No	62.5%	100%

p= 0.05

Conclusion

- Only 37.5% of the patients made thromboprophylaxis when it is indicated
- 56% patients are exposed with a high risk of VTD.
- Only 31% immobilized patients made thromboprophylaxis
- In general, low level of thromboprophylaxis

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RIETE Registry

- RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) is an ongoing, international multicentre, prospective registry of consecutive patients presenting with symptomatic acute venous thromboembolism (VTD).
- Database: 45000 patients
- It started in Spain in 2001, and some years later the database was translated into English aimed to expand the Registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients.
- Data from this registry have been used to evaluate outcomes after acute VTD, such as the frequency of recurrent VTD, major bleeding and mortality, and risk factors for these outcomes.

RIETE Registry

Antipsychotic & VTD

- To assess the caractherisitics of patients who takes antipsychotic and had suffered a VTD
  - Analized outcomes
  - Bleedings
  - Relationship with other cardiovascular risk factors

Baseline chracteristics

	Antipsychotics	No antipsychotics	p value
Patients, N	**713**	**17,361**	
Clinic characteristics			
Age	70±16	60±19	<0.001
Gender (males)	278 (39%)	9,168 (53%)	<0.001
Weight	74±17	76±16	0.006
VTD outcome,			
DVT	280 (39%)	9,471 (55%)	<0.001
PE	289 (41%)	5,007 (29%)	
DVT & PE	144 (20%)	2,883 (17%)	
VTD risk factors,			
Surgery	62 (8.7%)	2,030 (12%)	0.014
Thromboprophylaxis	39 (63%)	1,222 (60%)	0.676
Inmobilized ≥ 4 days	281 (39%)	3,142 (18%)	<0.001
Thromboprophylaxis	61 (22%)	782 (25%)	0.235
Cancer	148 (21%)	2.840 (16%)	0.002
Estrogen therapy	39 (5.6%)	1,050 (6.2%)	0.530
Pregnancy	3 (0.4%)	438 (2.5%)	<0.001
Long travel	7 (1.0%)	585 (3.5%)	<0.001
None	250 (35%)	8,341 (48%)	<0.001
Previous VTD	100 (14%)	2,656 (15%)	0.354
Comorbility,			
Diabetes	120 (17%)	1,046 (12%)	<0.001
Statins	182 (27%)	1,513 (17%)	<0.001
Smoker	108 (16%)	1,532 (18%)	0.198
Hypertension	355 (51%)	3,264 (37%)	<0.001
Inmobilization by depression or dementia	113 (16%)	343 (2.0%)	<0.001
Thromboprophylaxis	4 (3.5%)	22 (6.4%)	0.253
Analysis ,			
Antiphospholipid	12 (6.3%)	442 (7.8%)	0.435
D-dimer: positive	443 (67%)	11,409 (68%)	0.016
D-dimer: negative	9 (1.4%)	530 (3.2%)	
D-dimer : not search	205 (31%)	4,772 (29%)	

	Antipsychotic	No antipsychotic	p value
Patients, N	**713**	**17,361**	
Initial therapy,			
LMWH	644 (90%)	15,469 (89%)	0.304
Mean LMWH dose (IU/kg/day)	173±46	178±40	0.001
UFH	43 (6.0%)	1.337 (7.7%)	0.100
Thrombolytics	0	2 (0.0%)	0.774
Inferior vena cava filter	12 (1.7%)	406 (2.3%)	0.254
Long-term therapy,			
Vitamin K antagonists	327 (46%)	10.281 (59%)	<0.001
LMWH	356 (50%)	6.422 (37%)	<0.001
Mean LMWH dose (IU/kg/day)	156±45	163±47	0.006
Outcome (90 days),			
Recurrent PE	5 (0.70%)	138 (0.79%)	0.782
Recurrent DVT	8 (1.12%)	177 (1.02%)	0.790
Recurrent VTE	13 (1.82%)	316 (1.82%)	0.995
Major bleeding	21 (2.95%)	243 (1.40%)	0.001
Overall death	73 (10.2%)	806 (4.64%)	<0.001
Causes death			
Fatal PE	8 (1.12%)	117 (0.67%)	0.157
Initial PE (% only PE patients)	7 (1.62%)	79 (1.00%)	0.237
Recurrent PE	1 (0.14%)	38 (0.22%)	0.657
Bleeding	3 (0.42%)	41 (0.24%)	0.327
Sudden, unexpected	4 (0.56%)	16 (0.09%)	<0.001
Disseminated cancer	15 (2.10%)	256 (1.47%)	0.175
Respiratory insufficiency	7 (0.98%)	59 (0.34%)	0.005
Heart failure	3 (0.42%)	24 (0.14%)	0.056
Infection	12 (1.68%)	56 (0.32%)	<0.001
Myocardial infarction	0	5 (0.03%)	0.650
Ischemic stroke	1 (0.14%)	12 (0.07%)	0.487
Renal insufficiency	1 (0.14%)	5 (0.03%)	0.109
Critical limb ischemia	1 (0.14%)	1 (0.00%)	0.001
Multiorganic failure	3 (0.42%)	30 (0.17%)	0.129
Diabetic coma	0	1 (0.00%)	0.839
Liver insufficiency	1 (0.14%)	4 (0.02%)	0.065
Intestinal occlusion	0	6 (0.03%)	0.620
Bronchoaspiration	9 (1.26%)	17 (0.10%)	<0.001
Mesenteric ischemia	0	3 (0.02%)	0.726
Other	1 (0.14%)	22 (0.13%)	0.921
Unknown	4 (0.56%)	131 (0.75%)	0.556

Summary

Summary

- VTD in psychiatric patients
  - Own psychiatric illnes
    - *Raised thrombogenics markers*
      - » *Homocysteine*
      - » *Factor VIII*
      - » *sP-selectin*
    - *Antiphospholipid antibodies*
  - Antipsychotics
    - *Second generation*
    - *Haloperidol & clorpromacine*
  - Classic risk factors
    - *Obesity*
    - *Inmobilization*

- VTD & antipsychotics
  - No stop treatment but change to less thrombotic power
  - Treatment by general VTD guides as a general population.
  - Not routinely thromboprophylaxis in acute psychotic outbreak except need inmobilization with or without sedation .
  - Thromboprophylaxis if medical or surgery condition
  - Not routinely thrombophilia screening.

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Thank you