Pharmacological treatment of pulmonary embolism

Ghada Kazamel MD
NHI
2018

Case 1

- A 30 y woman presents to the ER with abrupt onset of dyspnea.
  - pleuritic chest pain
  - previously had radical mastectomy , computer programmer.
  - recently traveled by train to aswan
- On exam, she is uncomfortable, anxious and breathing rapidly.
  - pulse 105/min
  - BP 110/70
  - breathing 36/minute
- Laboratory studies are normal, except for arterial blood gases.
  - pH 7.48, pCO_2 30 mmHg, pO_2 75 mmHg (on 40% O_2)

What is the diagnosis?

Case 2

- A 34 yo man presents with the abrupt onset of shock (low blood pressure).
  - Healthy athlete until 16 days previously.
  - Severe spinal cord injury playing football, resulting in paraplegia.
  - Now in rehabilitation center, making good progress overall.
- Physical Exam:
  - General: Ashen appearing with a clouded sensorium.
  - Pulse 120/min and weak.
  - BP 74/50
  - Breathing 28/minute, Lungs are clear.
- Laboratory Studies:
  - Normal
  - ABG: pH 7.19, PCO_2 28 mmHg, PO_2 52 mmHg (on 40% O_2)

Diagnostic investigations

In patients presenting with signs or symptoms of PE, carry out the following to exclude other causes:

- an assessment of their general medical history
- a physical examination and
- a chest X-ray

If PE suspected use the two-level PE Wells score

Two-level PE Wells score

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation more than 3 days/surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment/treated in the past 6 months/palliative)	1
Clinical probability simplified scores	
PE **likely**	More than 4
PE **unlikely**	4 or less

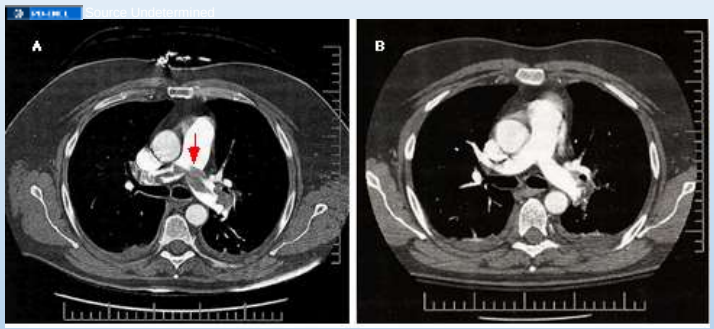
[a] Adapted with permission from Wells PS et al. (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thrombosis and Haemostasis 83: 416–20

Pretest probability: Low (<2 points),Intermediate (2-6 points),High (>6 points)

Diagnostic investigations

Two-level PE Wells score	
PE likely	PE unlikely
1. Offer immediate CTPA	1. Offer a D-dimer test
2. If CTPA not immediately available offer interim parenteral anticoagulant therapy followed by CTPA	2. If D-dimer positive offer immediate CTPA
3. If CTPA negative and DVT suspected consider proximal leg vein ultrasound	3. If CTPA not immediately available offer interim parenteral anticoagulant therapy followed by CTPA

Diagnostic Tests: CT Angiography



Saddle Embolus → Resolution
Thrombolysis

An approach to Prophylaxis

our priority is determine patient at risk

- Low risk (<40 years old, ambulating, minor surgery)
- Moderate risk (>40 years old, abdominal, pelvic or thoracic surgery)
- High risk (>60years old, prior DVT or PE malignancy, orthopedic surgery hypercoagulability state).

then prophylaxis of choice

- Encourage all patients ambulation as soon as possible
- Low risk patient don't need prophylaxis.
- Moderate risk pneumatic compression boot or low dose heparin prophylaxis.
- High risk combination of pneumatic compression boot and low dose heparin prophylaxis or Dextran.

Coumadine or IVC filter are considered.

Ophthalmology or neurosurgery patient are NOT candidates for prophylaxis.

Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Workup for PE

- In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).
- patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).
- In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

we suggest LMWH or fondaparinux over IV UFH (Grade 1A) and over SC UFH . The efficacy of heparin therapy depends on achieving a critical therapeutic level of heparin within the first 24 hours of treatment. The critical therapeutic level of heparin is 1.5 times the baseline control value or the upper limit of normal range of the activated partial thromboplastin time (aPTT).

Remarks: cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered

Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

UFH therapy

- If IV UFH is chosen, an initial bolus of 80 U/kg or 5000 U followed by an infusion of 18 U/kg/h or 1300 U/h should be given, with the goal of rapidly achieving and maintaining the aPTT at levels that correspond to therapeutic heparin levels. Fixed-dose and monitored regimens of subcutaneous UFH are available and are acceptable alternatives.

Low-molecular-weight heparin therapy

- LMWH can be administered safely in an outpatient setting. This has lead to the development of programs in which clinically stable patients with pulmonary embolism are treated at home, at substantial cost savings.
- An international, open-label, randomized trial compared outpatient and inpatient treatment (both using the LMWH enoxaparin as initial therapy) of low-risk patients with acute pulmonary embolism and concluded that outpatient treatment was non inferior to inpatient treatment.

Lancet. Jul 2 2011;378(9785):41-8

Fondaparinux

- Fondaparinux is a synthetic polysaccharide derived from the antithrombin binding region of heparin. Fondaparinux catalyzes factor Xa inactivation by antithrombin without inhibiting thrombin.
- Fondaparinux has not been directly compared with subcutaneous UFH or LMWH.
- However, once-daily fondaparinux was found to have similar rates of recurrent pulmonary embolism, bleeding, and death as IV UFH, according to one randomized open-label study of 2213 patients with symptomatic pulmonary embolism.

Br J Haematol. Nov 2005;131(3):301-12.

Duration: The ACCP recommended

- Initial treatment with low–molecular-weight heparin, unfractionated heparin or fondaparinux for at least five days in patients with acute DVT or pulmonary embolism; this is plus vitamin K antagonists (VKA). The heparin preparations should be discontinued when international normalized ratio reaches ≥2 for at least 24 hours.

Duration of anticoagulation therapy

- A patient with a first thromboembolic event occurring in the setting of reversible risk factors, such as immobilization, surgery, or trauma, should receive warfarin therapy for at least 3 months.
- No difference in the rate of recurrence was observed in either of 2 studies comparing 3 versus 6 months of anticoagulant therapy in patients with idiopathic (or unprovoked) first event.

BMJ. Mar 31 2007;334(7595):674

"The current recommendation is anticoagulation for at least 3 months in these patients; the need for extending the duration of anticoagulation should be reevaluated at that time."

Duration of anticoagulation therapy

- The current ACCP guidelines recommend that all patients with unprovoked pulmonary embolism should undergo a risk-to-benefit evaluation to determine if long-term therapy is needed (grade 1C). Long-term treatment is recommended for these patients who do not have risk factors for bleeding and in whom accurate anticoagulant monitoring is possible (grade 1A).

Duration of anticoagulation therapy

- Patients who have pulmonary embolism and preexisting irreversible risk factors, such as deficiency of antithrombin III, protein S and C, factor V Leiden mutation, or the presence of antiphospholipid antibodies, should be placed on long-term anticoagulation.

Recommendations for Fibrinolysis for Acute PE

- 1. Fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications *(Class IIa; Level of Evidence B).*
- 2. Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications *(Class IIb; Level of Evidence C).*
- 3. Fibrinolysis is not recommended for patients with low-risk PE *(Class III; Level of Evidence B) or* submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening *(Class III; Level of Evidence B).*
- 4. Fibrinolysis is not recommended for undifferentiated cardiac arrest *(Class III; Level of Evidence B).*

Systemic Thrombolytic Therapy for Patients With PE

In patients with acute PE, when a thrombolytic agent is used,
Streptokinase, Urokinase,Tissue plasminogen activator
we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).

In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

Catheter-Based Thrombus Removal for the Initial Treatment of Patients With PE

In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

NOAC

- Non-vitamin K oral anticoagulants include dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). are "*direct* and *specific* inhibitors of a single coagulation factor" and have the characteristics of: rapid onset of action (peak plasma levels in 2-4 hours); relatively short half-lives (8-12 hours); lack of significant food interactions; and fewer drug interactions compared with traditional VKAs.[14]
- In addition, the risk of bleeding (especially intracranial bleeds) appears to be less with NOAC therapy compared with VKA therapy
- Of the four available NOAC options, apixaban and rivaroxaban have the advantage of not requiring pre-treatment with LMWH (enoxaparin, etc)
- Antidote: In October 2015, the FDA approval of an antidote for dabigatran. Idarucizumab (Praxbind)

IVCF

- **IVC Filter**:

If anticoagulation is contraindicated (ie, active GI bleed, intracranial neoplasm, know bleeding diathesis), if thrombus formed despite adequate anticoagulation, or with a large burden of thrombosis in the LE that could be fatal if emblazed

Early vs Standard Discharge of Patients With Acute PE

In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).
patients must meet the following criteria to be considered suitable for treatment of acute PE at home: clinically stable with good cardiac reserve; no contraindications (i.e., recent bleeding episode), severe hepatic or renal disease, or severe thrombocytopenia (i.e., $<70{,}000/mm^3$); expectation of treatment compliance; and patient feels well enough to be treated at home.

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

Questions ??