Three-part question

[In adults who present to the emergency department with suspected acute opiate overdose] is [reversal with naloxone] [diagnostic ONLY of opiate use]?

Search strategy

Medline 1966 to August 2006 using the OVID interface. Embase 1980 to 2006. CINHAL 1982 to 2006. [{exp DIAGNOSIS/OR DIAGNOSIS.mp. OR sensitiv\$.mp OR specifit\$.mp} AND {exp. naloxone OR Narcan.mp OR opiate antagonist.mp} AND {exp. Narcotics AND exp. Overdose}] Limit to humans and English

Cochrane Database 2006: naloxone and overdose

Search outcome

Medline: 757 results were found, of which 3 were relevant. Embase: 95 results were found. No further relevant papers. CINHAL: 14 papers were found. No further relevant papers. The Cochrane library: No new papers found.

Relevant papers

Comments

Naloxone is often used, both for its diagnostic and therapeutic use, in patients presumed to have taken opiates. This BET looked at the question of whether naloxone can improve the decreased Glasgow Coma Score and respiratory depression associated with other conditions, especially other overdoses. These three studies, although not specifically written to answer the question, seem to show that a proportion of patients who have not taken opiate may respond to naloxone. However, not all the patients underwent toxicological analysis to give a final definite diagnosis, and some patients who seemed to respond to narcan but were documented as non-opiate overdoses may have just coincidentally improved. There seems to be no detrimental effects from the use of narcan in non-opiate overdoses.

Clinical bottomline

The evidence suggests that opioid antagonists are able to reverse symptoms, such as altered consciousness, in patients who have not taken an overdose of opiates. It is unclear in which conditions or circumstances this occurs.

Kaplan JL, Marsi JA, Calabro JJ, *et al*. Double-blind randomised study of nalmeferene and naloxone in emergency department patients with narcotic overdose. *Ann Emerg Med* 1999;**34**:42–50.

Hoffman JR, Schringer DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991;**20**:246–52.

Sporer KA, Firstone J, Issacs SM. Out-of-hospital treatment of opioid overdose in an urban setting. *Acad Emerg Med* 1996;**3**:660–7.

Pregnancy-associated plasma protein A: a novel cardiac marker with promise

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doi: 10.1136/emj.2006.042184

Three-part question

In [patients with chest pain of suspected cardiac origin] does [measurement of serum PAPP-A [pregnancy-associated plasma protein A] on admission] allow [exclusion of acute coronary syndromes]?

Clinical scenario

A 45-year-old abusive, intoxicated recurrent attender complains of central chest pain of 2 h duration. His initial electrocardiogram is normal. Your gut feeling is that he does not have an acute coronary syndrome. You are reluctant to admit him for troponin estimation at 12 h, but wonder if you ought to risk discharge without further investigation. Having heard about PAPP-A, a promising cardiac marker, you wonder if the evidence is sufficient to allow it to be used clinically in this situation.

Search strategy

Medline 1966–week 2 in September 2006 using the Ovid interface, Embase 1980–week 36 in 2006 using the Ovid interface, and the *Cochrane Library*, 2006 Issue 3. Medline: [exp Myocardial Infarction/OR exp Angina, Unstable/OR unstable angina.mp. OR (myocard\$ adj infarct\$).mp. OR (myocard\$ adj ischaem\$).mp. OR (myocard\$ adj ischaem\$).mp. OR acute coronary syndrome.mp. OR MI.mp. OR AMI.mp. OR ACS.mp. OR heart attack\$.mp.] AND [exp Pregnancy Associated Plasma Protein-A/OR PAPP-A.mp.]. Embase: [exp Myocardial Infarction/OR exp Angina, Unstable/OR exp Heart Attack/OR exp Coronary Thrombosis/OR (myocard\$ adj (ischaem\$ OR ischem\$ OR infarct\$)).mp. OR MI.mp. OR heart attack\$.mp. OR ACS.mp.] AND [PAPP-A.mp. OR exp Pregnancy Associated Plasma Protein A/] limit to human and English language. *Cochrane Library*: (MeSH Pregnancy Associated Plasma Protein A) OR PAPP-A (Search All Fields).

Search outcome

Altogether 35 papers were identified using Medline, 59 using Embase and 10 using the *Cochrane Library*. Five relevant papers were identified using both Medline and Embase, whereas no relevant papers were identified using the *Cochrane Library*.

Comments

PAPP-A was first found in the serum of pregnant women and has been used as a marker of Down's syndrome in the first trimester. Its abundant expression has been shown in unstable but not stable atherosclerotic plaques, and raised serum PAPP-A levels are associated with complex stenoses on coronary angiography.

Interestingly, although Bayes-Genis *et al* identified a marked increase in PAPP-A levels in patients with both myocardial infarction and unstable angina, the levels did not correlate with the number of coronary stenoses identified at angiography. This may mean that PAPP-A helps to identify soft, inflammatory plaques that are vulnerable to rupture or erosion. These plaques are more likely to undergo outward remodelling, leading to little or no arterial stenosis, while being responsible for most acute coronary syndromes (Little *et al*, 1988).

Although early research suggests that PAPP-A may be insufficiently sensitive to detect myocardial infarction at presentation to the emergency department, it remains a promising marker for incorporation into a multimarker strategy at patient presentation. Studies consistently show that PAPP-A may predict adverse events on clinical follow-up. Levels do not correlate with those of troponins, which may mean that PAPP-A helps to identify patients with unstable coronary disease without infarction. Although current diagnostic strategies enable sensitive detection of infarction, the identification of patients at risk of infarction in the near future would be of tremendous benefit.

Further research into PAPP-A when incorporated into a multimarker strategy for the risk stratification of patients with suspected acute coronary syndrome is warranted.

Table 4

Authors, date, country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Bayes-Genis <i>et al.</i> ¹ 2001, USA	17 patients with acute myocardial infarction, 20 with unstable angina, 19 with stable angina, and 13 age-matched controls without clinical or angiographic evidence of coronary atherosclerosis; all patients were scheduled to undergo coronary angiography; consecutive patients were recruited	Prospective cohort study	Median PAPP-A levels in controls v those with stable angina	Higher PAPP-A levels in stable angina but not statistically significant; controls 7.4 (range 3.8–10.4) mIU/L; stable angina 8.4 (range 4.4–22.5 mIU/L); $p=0.07$	Although the methods used are useful for identifying promising markers for further identification, they are suboptimal to assess diagnostic efficacy in clinical practice; recruitment of an undifferentiated group of patients, all of whom undergo the same gold standard diagnostic test would be necessary to achieve this Specificity cannot be calculated for the same reason
Lund <i>et al.</i> ² 2003, Finland	136 patients who had presented to the emergency department with suspected ACS and tested negative for troponin I during the first 24 h	Prospective observational cohort	Median PAPP-A levels in those with unstable angina v controls and in those with stable angina	Significantly higher PAPP-A levels in patients with unstable angina when compared with both controls ($p<0.001$) and those with stable angina ($p<0.001$); in patients with unstable angina 14.9 (range 6.3–63.4) mIU/L	
Laterza <i>et al.</i> ³ 2004, USA	Blood was sent for PAPP-A testing at admission, after 6–12 h and after 24 h; patients were followed up for 6 months	Prospective observational cohort	Median PAPP-A levels in patients with myocardial infarction v controls and those with stable angina	Significantly higher PAPP-A levels in myocardial infarction, compared with both controls ($p<0.001$) and those with stable angina ($p<0.001$); in patients with myocardial infarction 20.6 (range 9.2–46.6) mIU/L	Small numbers
Dominguez-Rodriguez <i>et al.</i> ⁴ 2004, Canada	346 patients presenting to the emergency department with symptoms suggestive of ACS	Prospective diagnostic cohort	Median PAPP-A levels in patients with myocardial infarction v those with unstable angina	No significant difference ($p=0.75$) in PAPP-A levels	
Heeschen <i>et al.</i> ⁵ 2005, The Netherlands	547 patients with available baseline blood samples, who had been enrolled in the CAPTURE trial with acute coronary syndrome (recurrent chest pain at rest associated with ECG changes during treatment with intravenous nitroglycerin and heparin). All patients underwent coronary angiography before randomisation, which demonstrated a stenosis $\geq 70\%$ and subsequently underwent angioplasty. The CAPTURE trial had randomised patients to receive either abciximab or placebo. The abciximab group was excluded from this study as abciximab has been shown to interact with troponin T and sCD40L, both of which were also measured in this study. Blood had been taken 8.7 ± 4.9 hours after the last episode of chest pain. A second group of 626 consecutive patients presenting to the Emergency Department with acute chest pain <12 hours and had no ST elevation was then recruited to prospectively validate the predictive value of PAPP-A. Blood was taken 5.1 ± 3.4 hours after symptom onset. Patients were divided into quintiles with regard to their PAPP-A results for analysis	Observational cohort, initially retrospective but with prospective validation	Correlation of PAPP-A with troponin T Cardiac events at follow up in clinical trial group Cardiac events at 30 days in the Emergency Room group	Poor correlation ($r=0.11$) in the clinical trial group No significant difference between the quintiles at 24 h ($p=0.69$); significantly increased incidence with rising PAPP-A at 72 hours ($p=0.019$), 30 days ($p=0.008$) and 6 months ($p=0.004$) Patients with PAPP-A >12.6 mIU/L had significantly more events than patients with low PAPP-A (16.9% vs. 7.9%, adjusted odds ratio 2.32, $p=0.008$)	Results are not reported in a clinically meaningful manner. There is insufficient data to allow the calculation of sensitivities and specificities. The use of a cut-off value for PAPP-A to aid diagnosis or exclusion of acute coronary syndrome was not prospectively validated

ACS, acute coronary syndrome; CCU, cardiac care unit; CK, creatine kinase; ECG, electrocardiogram; LR, logistic regression; MI, myocardial infarction; NPV, negative predictive value; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value; ROC, receiver-operator characteristic; STEMI, ST elevation myocardial infarction.

Clinical bottomline

PAPP-A may be insufficiently sensitive for the detection of myocardial infarction at presentation to the emergency department. However, it is a promising marker for the detection of unstable coronary disease and may have tremendous potential as a prognostic marker, especially if incorporated into a multimarker strategy.

- 1 Bayes-Genis A, Conover CA, Overgaard MT, *et al.* Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. *N Engl J Med* 2001;**345**:1022–9.
- 2 Lund J, Qin QP, Ilva T, *et al.* Circulating pregnancy-associated plasma protein A predicts outcome in patients with acute coronary syndrome but no troponin I elevation. *Circulation* 2003;**108**:1924–6.

- 3 Laterza OF, Cameron SJ, Chappell D, *et al.* Evaluation of pregnancy-associated plasma protein A as a prognostic indicator in acute coronary syndrome patients. *Clin Chim Acta* 2004;**348**:163–9.
- 4 Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez M, *et al.* Circulating pregnancy-associated plasma protein A is not an early marker of acute myocardial infarction. *Clin Biochem* 2005;**38**:180–2.
- 5 Heeschen C, Cimmeler S, Hamm CW, *et al.* Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes. *J Am Coll Cardiol* 2005;**45**:229–37.
- 6 Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome based on tests performed during the first and second trimesters. *N Engl J Med* 1999;**341**:461–7.
- 7 Cosin-Sales J, Christiansen M, Kaminski P, *et al.* Pregnancy-associated plasma protein A and its endogenous inhibitor, the proform of eosinophil major basic protein (proMBP), are related to complex stenosis morphology in patients with stable angina. *Circulation* 2004;**109**:1724–8.
- 8 Little WC, Constantinescu M, Applegate RJ, *et al.* Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;**78**:1157–66.