Täiskasvanute astma käsitlus esmatasandil
Tõendusmaterjali kokkuvõte

Kliiniline küsimus nr 13

1. *Kliinilise küsimuse tekst:* Kas astma diagnoosiga patsientidele, kellel on kaasuv krooniline skeleti-lihassüsteemi haigus, tohib kasutada mittesteroidseid põletikuvastaseid ravimeid (MSPVA) vs paratsetamool?

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Enamusel aspiriini indutseeritud astma patsientidel esines risttundlikkust käsimüügi mitte-põletikuvastastele ravimile: ibuprofeen, 98%; naprokseen, 100% ja diklofenak, 93%. Paratsetamoolile esines risttundlikkus ainult 7%-l sellest patsiendigrupist (Jenkins 2004).

Väikesel osal MSPVA talumatusega astma patsientidest esineb suurtes annustes paratsetamooli kasutamisel lühiajaline hingamisfunktsiooni halvenemine, kuid see pole sage ja ei ole seotud eluohtlike reaktsioonidega (Levy 2004).

Kuigi suures annuses (> 1000 mg) paratsetamooli kasutamisel oli oluline ristuv reaktsioon aspiriiniga sage (34%), oli reaktsiooniks kergesti mööduv bronhospasmi (ainult 22%-l) ja need olid üldiselt kerge kuluga. (Settipane1995)

20%-l astma patsientidest esineb aspiriini jt MSPVA-de talumatus.Seevastu paratsetamooli talub enamus astma patsientidest hästi ning see on harva seotud risttundlikkusega. (Jenkins 2000).

Paratsetamooli kasutamisel leiti positiivne seos astmaga. Astma šansisuhe patsientidel, kes polnud paratsetamooli kunagi kasutanud oli 1,06 (95% CI 0,77-1,45), vähekasutajatel (<kuus), 1,22 (0,87-1,72) igakuistel kasutajatel, 1. 79 (1,21-2,65), iganädalastel kasutajatel 2,38 (1,22-4,64) ja igapäevastel kasutajatel (p (trend) = 0,0002) . Seos esines nii aspiriini kasutajatel kui ka mittekasutajatel ja oli tugevam raskema haigusega juhtudel võrreldes kontrollgrupiga; suurema paratsetamooli kasutamisega juhud olid seotud raskema haiguse kuluga. Kontrollgrupiga võrdlusel ei esinenud aspiriini kasutamise sagedusel seost astmaga ega astma raskusastmega. Sagedased paratsetamooli kasutamise sagedusl oli positiivne seos nohuga, kuid aspiriini kasutamist ei olnud. (Shaheen 2000)

Lisaküsimus 2013 a viimasel töörühma koosolekul sekretariaadile: kui patsiendil aspiriin-indutseeritud astma JA südame isheemiatõbi , siis kas eelistatud on aspiriinile desensitiseerimine või klopidogreel?
Sekretariaadi vastus: pigem aspiriinile desensitiseerimine, eriarstlik konsultatsioon vajalik.

Otsing 06.02.2014: ("Platelet Aggregation Inhibitors"[Mesh] AND "Aspirin"[Mesh]) AND "Asthma"[Mesh] n=15, nendest viimase 10 a jooksul ilmunud ja asjakohased:
Pattanaik 2012: ülevaateartikkel, et aspiriinile ülitundlikkuse korral südame isheemiatõvega patsiendil on aspiriinile desensitiseerimine võimalik
Cardona 2009: kolme desensitiseerimise haigusjuhu kirjeldus
Shaker 2008: desentitiseerimine on USAs kulutõhusam valik kui ravi klopidogreeliga
Collapudi 2004: ülevaateartikkel desensitiseerimisest aspiriinile.

Eraldi otsing klopidogreeli kohta 06.02.2014 kahes variandis: "Clopidogrel"[Mesh] AND "Asthma"[Mesh] AND ((Randomized Controlled Trial[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp]) AND "2004/02/10"[PDat] : "2014/02/06"[PDat])= vasteid ei ole
"Platelet Aggregation Inhibitors"[Mesh] AND "Asthma"[Mesh] AND ((Randomized Controlled Trial[ptyp] OR systematic[sb] OR Meta-Analysis[ptyp]) AND "2004/02/10"[PDat] : "2014/02/06"[PDat]): 2 vastet, nendest üks puudutav COX-2 inhibiitorid ning teine on Collapudi 2004 ülevaateartikkel (vt eespool)

Ravijuhendid

Kokkuvõte ravijuhendites leiduvatest soovitustest:

Ravijuhendid soovitavad vältida atsetüülsalitsüülhappe jt MSPVA-de kasutamist täiskasvanud patsientidel, kellel on raske püsiv astma, ninapolüüp või ülitundliikus atsetüülsalitsüülhappe või teisele MSPVA-le. Selle asemel soovitakse kasutada väikese annuses paracetamooli (<650 mg individuaalne doos),

GINA: Generally asthma patients, especially those with adult onset of asthma and associated upper airway disease (nasal polypsis), should be counseled to avoid NSAIDs taking acetominophen/paracetamol instead.

Where an NSAID is indicated, a cyclooxygenase-2 (COX-2) inhibitor may be considered with appropriate physician supervision and observation at least one hour after administration (Evidence B).

For NSAID sensitive patients with asthma who require NSAID for other medical conditions, desensitization may be considered in the hospital under the care of specialist.

ERP 2 2007:

Adult patients who have severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or NSAID should be counseled regarding the risk of severe and even fatal exacerbations from using these drugs **(Evidence C).**

Recommendation: Clinicians query adult patients who have asthma regarding prescription of bronchoconstriction by aspirin or other NSAIDs **(Evidence C)**

If patients have experienced a reaction to any of these drugs, they should be informed of the potential for all of these drugs to precipitate severe and even fatal exacerbations. Adult patients who have severe persistent asthma or nasal polyp s should be counseled regarding the risk of using these drugs **(Evidence C).**

Alternatives to aspirin that usually do not cause acute bronchoconstriction in aspirin-sensitive patients include acetaminophen (7 % cross-sensitivity) (Jenkins et al. 2004), salsalate (Settipane et al 1995, Sczceklik et al 1977) or the COX-2 inhibitor celecoxib (Gyllfors et al 2003). Aspirin desensitization treatment, followed by daily aspirin is a potential option to decrease disease activity and reduce corticosteroid requirements (Berges- Gimeno et al 2003a,b)

GEMA:

Patients must be correctly diagnosed, either on the basis of obvious clinical history (various reactions to different NSAIDs) or an oral challenge, which can be substituted in serious cases by bronchial or nasal inhalatory challenge. The best alternative analgesic agent in these patients is paracetamol administrated at less than 650 mg per individual dose, given that some patients may have bronchospastic crises and these occur more often if high doses are used. Opiats such as tramadol or codeine, are also regarded as safe alternative

painkillers. Selective (meloxicam) or specific (celecoxib, etoricoxib) COX-2 inhibitors could be another alternative, although before recommending the , it is advisable to confirm patient tolerance. This type of test should be conducted in centers with experience in this field {c].

VaDoD 2009

NSAID and aspirin use in patient with nasal polyps , severe persistent asthma, or NSAID/ASA sensitivity should be strictly avoided.[B]

NSAID and aspirin avoidancde prevents attacks ib sensitive patients souce NHLBI, 2007; LE II; QE - fair; SR - B.)

Süstemaatilised ülevaated

Kokkuvõte	**Viide kirjandusallikale**
OBJECTIVE: To reassess the prevalence of aspirin induced asthma and other issues related to the syndrome. DATA SOURCES: Biosis, SciSearch (1990 to March 2002), Embase (1974 to March 2002), Medline (1966 to March 2002), Toxline, Derwent Drug File (1964 to March 2002), Conference Papers Index and Inside Conferences, Int'l Pharmaceutical Abstracts, Pharma-Online (1978 to March 2002). SELECTION CRITERIA: Study type, patient population, and outcome measures. Review was restricted to respiratory responses to analgesics available without prescription. RESULTS: The prevalence of aspirin induced asthma was highest when determined by oral provocation testing (adults 21%, 95% confidence interval 14% to 29%; children 5%, 0% to 14%) than by verbal history (adults 3%, 2% to 4%; children 2%, 1% to 3%). **Cross sensitivity to doses of over the counter non-steroidal anti-inflammatory drugs was present in most patients with aspirin induced asthma: ibuprofen, 98%; naproxen, 100%; and diclofenac, 93%. The incidence of cross sensitivity to paracetamol among such patients was only 7%.** CONCLUSIONS: Aspirin induced asthma in adults is more prevalent than previously suggested. When there is a clinical necessity to use aspirin or a non-steroidal anti-inflammatory drug and there is uncertainty about safety, oral provocation testing should be performed.	Jenkins C, Costello J, Hodge L.“Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice.“˅ BMJ. 2004 Feb 21;328(7437):434. http://www.ncbi.nlm.nih.gov/pubmed/14976098
Aspirin (acetylsalicylic acid) and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause deterioration in respiratory function in approximately 10% of adults with asthma and a smaller proportion of children with asthma. We propose evidence-based guidelines for the safe use of NSAIDs in individuals with asthma following systematic review of data from the last 10 years relevant to the use of these drugs in such patients. We would currently recommend that patients with asthma who are known to be intolerant of NSAIDs or who exhibit any of the high risk clinical features for intolerance to these drugs (severe asthma, nasal polyps or chronic rhinosinusitis) should use NSAIDs only under close medical supervision. In those with high risk features formal aspirin provocation testing would be recommended prior to the therapeutic use of NSAIDs. Those individuals with asthma who regularly use NSAIDs can continue to do so but should be warned that intolerance to NSAIDs can develop late in life. Lack of relevant experimental evidence precludes the production of evidence-based guidelines for the group of patients with asthma who do not exhibit high risk clinical features and who have never before used NSAIDs. We	Ülevaade (otsingustrateegia kirjeldatud) Levy S, Volans G. „The use of analgesics in patients with asthma.“ Drug Saf. 2001;24(11):829-41.http://www.ncbi.nlm.nih.gov/pubmed/11665870

would currently recommend that this group be treated as potentially intolerant to NSAIDs and use of these drugs can only be recommended under medical supervision but note that further studies and clinical experience could be expected to relax this restriction for many patients. Recent data have suggested that frequent use of paracetamol (acetaminophen) may contribute to a deterioration of respiratory function in asthma. **A small proportion of patients with asthma who are NSAID-intolerant experience short-lived deterioration in respiratory function with the use of high doses of paracetamol but this is uncommon and has not been implicated in life-threatening reactions. Routine warnings about paracetamol use in asthma are, therefore, not warranted.** Medical personnel, however, should be aware of the potential for worsening of symptoms in some individuals with asthma using paracetamol and institute formal investigation or withdrawal of the drug if they suspect such a reaction	

Viited

Pubmed otsingustrateegia (("Asthma"[Mesh]) AND "Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) AND "Acetaminophen"[Mesh]

Kokkuvõte (abstrakt või kokkuvõtlikum info)	**Viide kirjandusallikale**
Aspiriini ülitundlikkusega patsientidel tuleks vältida suures koguses paracetamooli (>1000mg) kasutust OBJECTIVE: Cross-sensitivity between aspirin and acetaminophen in aspirin-sensitive asthmatic patients has been reported with frequencies ranging from 0% to 29%. The relationship is dose-dependent for acetaminophen challenges, ranging between 300 and 100 mg. METHODS: To determine the prevalence of cross-sensitivity to high-dose acetaminophen, we performed single-blind acetaminophen oral challenges with 1000 mg and 1500 mg in 50 aspirin-sensitive asthmatic patients and in 20 non-aspirin-sensitive asthmatic control subjects. RESULTS: Overall, 17 of 50 (34%) of aspirin-sensitive asthmatic patients reacted to acetaminophen in doses of 1000 to 1500 mg (95% confidence interval: 20% to 49%). By contrast, none of the 20 non-aspirin-sensitive asthmatic patients reacted to acetaminophen (95% confidence interval: 0% to 14%). This difference was highly significant (p = 0.0013), supporting the hypothesis that cross-sensitivity between aspirin and acetaminophen is unique in aspirin-sensitive asthmatic patients. CONCLUSION: **Although high-dose (> 1000 mg) acetaminophen cross-reactions with aspirin were significant with respect to frequency (34%), such reactions included easily reversed bronchospasm in only 22%, and were generally mild. We recommended that high doses of acetaminophen (1000 mg or greater) should be avoided in aspirin-sensitive asthmatic patients.**	Settipane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD „Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects.“J Allergy Clin Immunol. 1995 Oct;96(4):480-5. http://www.ncbi.nlm.nih.gov/pubmed/7560658
Asthma is a common condition, affecting approximately 7% of people worldwide. However, the prevalence varies among countries, and in Australia, asthma affects 10% of adults and approximately 20% of children. For some of these patients, ingredients in some over-the-counter analgesics may pose problems. Aspirin sensitivity, defined as urticaria, angioedema, or rhinitis after aspirin ingestion, affects only 0.3% of the general population. However, certain patient groups, such as asthmatics, are at an increased risk, with reports of an	Jenkins C „Recommending analgesics for people with asthma“ Am J Ther. 2000

incidence as high as 20% in this patient population. This phenomenon is not restricted to aspirin, as all nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the enzyme cyclooxygenase display a high incidence of cross-sensitivity. **In contrast, paracetamol (acetaminophen) is well tolerated by the majority of people with asthma and is seldom associated with cross-sensitivity**. Determining who is likely to be affected is difficult because the sequence of symptoms is hard to predict, and patients often do not associate an asthma attack with the use of aspirin or an NSAID. The only definitive way to diagnose sensitivity is by provocation tests. In view of these difficulties, it is important for health care practitioners to take a pro-active stance by asking questions to determine whether aspirin sensitivity is a problem, counseling people about the risks, and helping them make an appropriate analgesic choice.	Mar;7(2):55-61 http://www.ncbi.nlm.nih.gov/pubmed/11319574
METHODS: Information was collected on the use of analgesics as part of a population based case-control study of dietary antioxidants and asthma in adults aged 16-49 years registered with 40 general practices in Greenwich, South London. The frequency of use of paracetamol and aspirin was compared in 664 individuals with asthma and in 910 without asthma. Asthma was defined by positive responses to questions about asthma attacks, asthma medication, or waking at night with shortness of breath. The association between analgesic use and severity of disease amongst asthma cases, as measured by a quality of life score, was also examined. RESULTS: Paracetamol use was positively associated with asthma. After controlling for potential confounding factors the odds ratio for asthma, compared with never users, was 1.06 (95% CI 0.77 to 1.45) in infrequent users (<monthly), 1.22 (0.87 to 1.72) in monthly users, 1. 79 (1.21 to 2.65) in weekly users, and 2.38 (1.22 to 4.64) in daily users (p (trend) = 0.0002). This association was present in users and non-users of aspirin and was stronger when cases with more severe disease were compared with controls; amongst cases increasing paracetamol use was associated with more severe disease. Frequency of aspirin use was not associated with asthma when cases as a whole were compared with controls, nor with severity of asthma amongst cases. Frequent paracetamol use was positively associated with rhinitis, but aspirin use was not. CONCLUSIONS: **Frequent use of paracetamol may contribute to asthma morbidity and rhinitis in adults**.	Shaheen SO, Sterne JA, Songhurst CE, Burney PG. „Frequent paracetamol use and asthma in adults.“ Thorax. 2000 Apr;55(4):266-70 http://www.ncbi.nlm.nih.gov/pubmed/10722764

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