Journal meeting
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Ibuprofen Prevents Altitude Illness: A Randomized Controlled Trial for Prevention of Altitude Illness With Nonsteroidal Anti-inflammatories

- Annals *of Emergency Medicine*
- Article in press

Background

- 急性高山症(AMS)，常發生於攀登高於海拔2500m時，在不同的海拔及裝備下,AMS發生率介於25-75%。
- AMS的症狀:headache, sleep disturbance, fatigue, dizziness, nausea,vomiting, or anorexia,一般在抵達高海拔後的6-12小時發生，而緩慢的爬升可以減低發生率。
- 特殊情況下,必須急速爬升海拔,如:搜救、軍事活動、短期旅遊等,該如何預防?

研究目的

- AMS的病理機轉可能和血管擴張,發炎反應及BBB有關,有些研究已經證實glucocorticoid可以用來治療及預防AMS。
- 基於NSAID可抑制COX-1,2，而降低發炎反應的藥理作用，NSAID應該可以用來預防AMS，但先前的研究尚未有定論。
- 此研究的目的是評估ibuprofen，可否降低AMS的發生率和嚴重度。

方法

- 2010年7~8月間, 在California當地的 White Mountains。
- 健康且居住在低於海拔1240m的成年自願者,隨機接受ibuprofen 600 mg或placebom,1 # TID,從爬升(from 1240m to 3810m)的六小時前開始服用。
- 主要outcome為測量AMS的發生率和嚴重度。
- Prospective, double-blind, randomized, placebo-controlled trial
  - (Stanford University School of Medicine and University of California)

方法

- Inclusion:Email,廣告的方式招收自願參加者，參加者必須身體健康，居住在海拔1240m以下,可以在高海拔做一定程度的活動年齡介於18-65歲。
- Exclusion:懷孕,過去一周生活在1240m以上;或是使用 diuretics, steroids, or acetazolamide or NSAIDs,或平時就有AMS症狀,brain tumor,asthma,GI bleeding, 等。

Lake Louise Score (LLS) for the diagnosis of Acute Mountain Sickness (AMS)

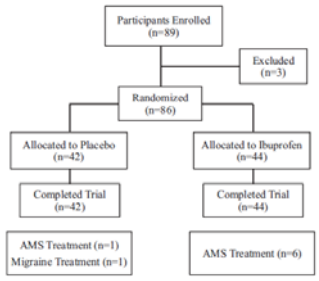
- A diagnosis of AMS is based on:
- 1. A rise in altitude within
- the last 4 days
- 2. Presence of a headache
- **PLUS**
- 3. Presence of at
- least one other symptom
- 4. A total score of 3 or
- more from the questions
- **Total score of:**
- 3 to 5 = mild AMS
- 6 or more = severe AMS

Headache	No headache	0	
	Mild headache	1	
	Moderate headache	2	
	Severe headache, incapacitating	3	
Gastrointestinal symptoms	None	0	
	Poor appetite or nausea	1	
	Moderate nausea &/or vomiting	2	
	Severe nausea &/or vomiting	3	
Fatigue &/or weakness	Not tired or weak	0	
	Mild fatigue/ weakness	1	
	Moderate fatigue/ weakness	2	
	Severe fatigue/ weakness	3	
Dizziness/lightheadedness	Not dizzy	0	
	Mild dizziness	1	
	Moderate dizziness	2	
	Severe dizziness, incapacitating	3	
Difficulty sleeping	Slept as well as usual	0	
	Did not sleep as well as usual	1	
	Woke many times, poor sleep	2	
	Could not sleep at all	3	
	TOTAL SCORE:		

結果

- 共86人完成研究:ibuprofen 組44人 (51%) placebo 組42 (49%)人。
- 兩組間的Baseline特性沒有差別。
- AMS發生率:ibuprofen組為43%，placebo組為69%。
- 發生AMS的嚴重度: ibuprofen組為3.2，placebo組為4.4。

結果



結果

Table 1. Baseline demographics.

Variable	Placebo, No. (%), N=42	Ibuprofen, No. (%), N=44	Difference in Estimates Between Treatment Groups, OR (95% CI)
Female sex	14 (33.3)	14 (31.8)	1.1 (0.4 to 2.6)
Age, y	34.8 (13.2)	38.4 (14.5)	3.7 (−2.3 to 9.6)*
Ethnicity			
White	35 (83.3)	32 (72.7)	1
Asian	5 (11.9)	10 (22.7)	2.2 (0.7 to 7.7)
Other	2 (4.8)	2 (4.6)	1.1 (0.2 to 8.2)
Home altitude: 0–300 m (990 ft)	41 (97.6)	43 (97.7)	1.0 (0.1 to 15.8)
Arrival route			
Yosemite	30 (71.4)	32 (72.7)	1
Los Angeles	8 (19.1)	3 (6.8)	0.4 (0.1 to 1.5)
Lake Tahoe	1 (2.4)	2 (4.5)	1.9 (0.2 to 21.8)
Other	3 (7.1)	7 (15.9)	2.2 (0.6 to 9.2)
History of altitude illness	5 (11.9)	2 (4.6)	0.4 (0.1 to 1.9)
History of headaches	2 (4.8)	5 (11.4)	2.6 (0.5 to 14)

OR, Odds ratio.
*Reported as the mean difference in percentage (95% CI).

結果

Table 2. Primary outcomes.

Variables	Placebo, N=42	Ibuprofen, N=44	Difference in Estimates Between Treatment Groups, OR (95% CI)
AMS incidence (%)	29 (69)	19 (43)	0.3 (0.1–0.8)
AMS severity: peak LLQ score, mean (SD)	4.4 (2.6)	3.2 (2.4)	0.9 (0.3–3.0)*

LLQ, Lake Louise Questionnaire.
*Reported as the mean difference in percentage.

Table 3. Secondary outcomes.

Variables	Placebo, N=42	Ibuprofen, N=44	Difference in Proportions Between Treatment Groups, % (95% CI)
Headache severity change: VAS, mean (SD)	27.7 (24.9)	19.0 (18)	8.7 (−0.7 to 18)
SpO_2 change from baseline, mean (SD)	−13.1 (4.5)	−14.7 (4.9)	1.6 (−0.4 to 3.7)

VAS, Visual analog scale.

結果

Table 4. Prevalence of LLQ symptoms by subgroup.*

Variables	Study Participants	Placebo (%)	Ibuprofen (%)	Difference in Estimates Between Treatment Groups, OR (95% CI)
Headache	85	31 (75.6)	29 (65.9)	0.6 (0.2–1.6)
GI symptoms	84	19 (47.5)	10 (22.7)	0.3 (0.1–0.8)
Weakness	85	28 (68.3)	25 (56.8)	0.6 (0.3–1.5)
Dizziness	83	20 (51.3)	19 (43.2)	0.7 (0.3–1.7)
Sleeplessness	84	34 (82.9)	35 (81.4)	0.9 (0.3–2.8)

GI, Gastrointestinal.
*LLQ subgroup score of greater than 0 signified presence of the symptom. Participant number considers both second and third measurement; if the third was missing, the second measurement was used.

結論

- Ibuprofen能有效的降低AMS的發生率和嚴重度。

Limitation

- 研就開始前一晚,先在1240m處集合,水土不服?
- 環境的因素
- 受試者的生理因素
- 海拔爬升的速度,高度等

Disscussion

- Dexamethasone: hyperglycemia , adrenal suppression, delirium, depression, insomnia, and mania
- Acetazolamide:nausea, dizziness, and fatigue
- 研究顯示ibuprofen可以有效減輕AMS的嚴重度,但尚未達到預設的標準(Lake Louise Questionnaire降低2分以上)

Placebo-Controlled Trial of mantadine for Severe Traumatic Brain Injury

- *The* NEW ENGLAND *JOURNAL o f MEDICINE*
- n engl j med 366;9 nejm.org march 1, 2012

- Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D.,Kathleen Kalmar, Ph.D., Nancy Childs, M.D., Allen Khademi, M.D.,Bernd Eifert, M.D., David Long, M.D., Douglas I. Katz, M.D., Sooja Cho, M.D.,Stuart A. Yablon, M.D., Marianne Luther, M.D., Flora M. Hammond, M.D.,Annette Nordenbo, M.D., Paul Novak, O.T.R., Walt Mercer, Ph.D.,Petra Maurer-Karattup, Dr.Rer.Nat., and Mark Sherer, Ph.D.

背景

- 對於創傷性腦損傷後，長期意識障礙的患者，Amantadine hydrochloride是一個很常使用的藥物。
- 先前已有研究顯示此藥可以促進功能的恢復

方法

- 選取184名腦部創傷後4到16星期，正在復健中的患者(vegetative or minimally conscious state)
- 患者被隨機分配服用amantadine或placebo四星期的時間，停藥後追蹤兩周
- 利用Disability Rating Scale(0-29)來評估,用藥四星期後(primary outcome)，以及停藥兩星期(washout period)的情況

方法

- 三個國家的11 家醫院，Screen 1170個病人, enroll 184個介於16 to 65 歲，腦部外傷後4-16週復健中的患者(意識不好，DRS> 11)
- 前兩周100 mg BID，若第二週結束DRS沒有進步超過2分，則第三週150 mg BID,第四週200 mg BID，四周後停藥，持續追蹤到第六週結束。

Disability Rating Scale(0-29)

Category	Item	Instructions	Score
Arousability, Awareness and Responsivity	Eye Opening	0 = spontaneous 1 = to speech 2 = to pain 3 = none	
	Communication Ability	0 = oriented 1 = confused 2 = inappropriate 3 = incomprehensible 4 = none	
	Motor Response	0 = obeying 1 = localizing 2 = withdrawing 3 = flexing 4 = extending 5 = none	
Cognitive Ability for Self Care Activities	Feeding	0 = complete 1 = partial 2 = minimal 3 = none	
	Toileting	0 = complete 1 = partial 2 = minimal 3 = none	
	Grooming	0 = complete 1 = partial 2 = minimal 3 = none	
Dependence on Others	Level of Functioning	0 = completely independent 1 = independent in special environment 2 = mildly dependent 3 = moderately dependent 4 = markedly dependent 5 = totally dependent	
Psychosocial Adaptability	Employability	0 = not restricted 1 = selected jobs 2 = sheltered workshop (non-competitive) 3 = not employable	
Total DR Score			

COMA RECOVERY SCALE - REVISED

AUDITORY FUNCTION SCALE	**OROMOTOR/VERBAL FUNCTION SCALE**
4 - Consistent Movement to Command *	3 - Intelligible Verbalization *
3 - Reproducible Movement to Command *	2 - Vocalization/Oral Movement
2 - Localization to Sound	1 - Oral Reflexive Movement
1 - Auditory Startle	0 - None
0 - None	**COMMUNICATION SCALE**
VISUAL FUNCTION SCALE	2 - Functional: Accurate †
5 - Object Recognition *	1 - Non-Functional: Intentional *
4 - Object Localization: Reaching *	0 - None
3 - Visual Pursuit *	**AROUSAL SCALE**
2 - Fixation *	3 - Attention
1 - Visual Startle	2 - Eye Opening w/o Stimulation
0 - None	1 - Eye Opening with Stimulation
MOTOR FUNCTION SCALE	0 - Unarousable
6 - Functional Object Use †	**TOTAL SCORE**
5 - Automatic Motor Response *	
4 - Object Manipulation *	
3 - Localization to Noxious Stimulation *	
2 - Flexion Withdrawal	
1 - Abnormal Posturing	
0 - None/Flaccid	

結果

- 根據DRS score的測量，治療期間服用amantadine的患者明顯恢復較快 (difference in slope, 0.24 points per week; P = 0.007)
- Subgroup的分析, vegetative state和minimally conscious state的療效相似
- 停止服用amantadine的兩週，恢復的速度減慢，且明顯比Placebo組慢(difference in slope, 0.30 points per week; P = 0.02).
- 整體的改善在六週時，兩組無明顯差距

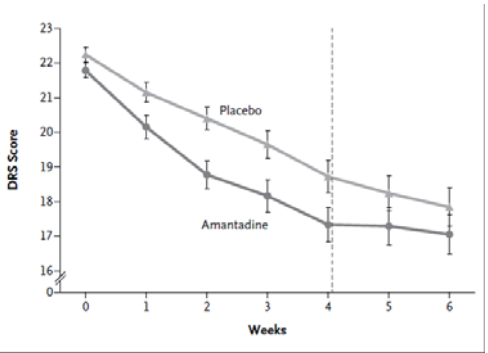


Figure 1. Mean Disability Rating Scale (DRS) Scores during the 6-Week Assessment Period, According to Study Group.

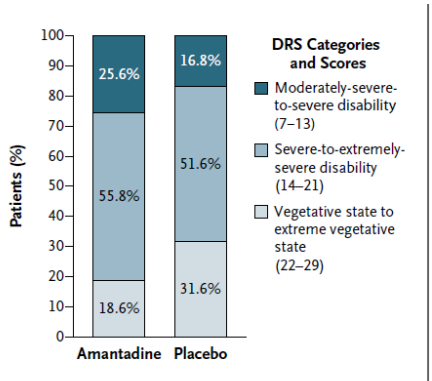


Figure 2. Post hoc Analysis of the Distribution of DRS Scores by Outcome Category.

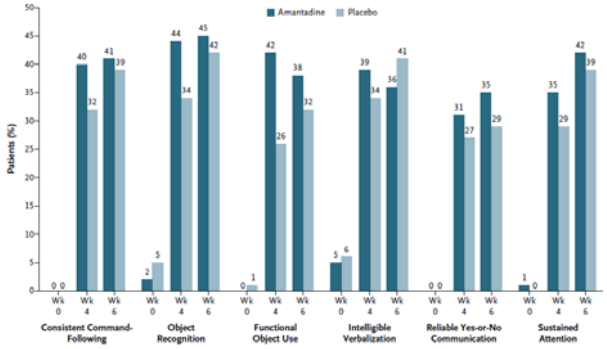


Table 2. Adverse Events, According to Treatment Group.*

Adverse Event	Amantadine (N=87)	Placebo (N=97)
	number (percent)	
Seizure	2 (2)	4 (4)
Changes on electroencephalography	1 (1)	0
Nausea	1 (1)	1 (1)
Vomiting	10 (11)	8 (8)
Constipation	2 (2)	3 (3)
Diarrhea	5 (6)	5 (5)
Other gastrointestinal event	4 (5)	11 (11)
Elevated liver-function tests†	3 (3)	3 (3)
Restlessness	7 (8)	9 (9)
Agitation	12 (14)	11 (11)
Insomnia	12 (14)	14 (14)
Involuntary muscle contractions	2 (2)	0
Hypertonia or spasticity	18 (21)	14 (14)
Other motor problems	1 (1)	1 (1)
Rash	5 (6)	6 (6)
Congestive heart failure	0	1 (1)

結論

- 在Amantadine的治療期間,可以加速創傷性腦損傷患者的功能恢復。

Disscussion & Limitation

- 患者的選擇可能會造成 bias。
- 每個醫院並沒有統一的復健標準。
- 無法確定是否可以改善長期的預後，或者只是短期加速恢復的速度。
- Amantadine最有效的使用時機，劑量，療程和非創傷患者是否有效， 需進一步研究。