

LE Magazine March 1997

ABSTRACTS

THE CLINICAL POTENTIAL OF ADEMETHIONINE (S-ADENOSYLMETHIONINE) IN NEUROLOGICAL DISORDERS

Bottiglieri T; Hyland K; Reynolds EH
Metabolic Disease Center, Baylor Research Institute, Dallas, Texas
Drugs (NEW ZEALAND) Aug 1994, 48 (2) p137-52,

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; SAME). SAME is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAME is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAME concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAME has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAME has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAME) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders. (115 Refs.)

BRAIN S-ADENOSYLMETHIONINE LEVELS ARE SEVERELY DECREASED IN ALZHEIMER'S DISEASE

Morrison LD; Smith DD; Kish SJ
Human Neurochemical Pathology Laboratory, Clarke Institute of Psychiatry, University of Toronto, Ontario, Canada / *J Neurochem (UNITED STATES) Sep 1996, 67 (3) p1328-31,*

S-Adenosylmethionine is an essential ubiquitous metabolite central to many biochemical pathways, including transmethylation and polyamine biosynthesis. Reduced CSF S-adenosylmethionine levels in Alzheimer's disease have been reported; however, no information is available regarding the status of S-adenosylmethionine or S-adenosylmethionine-dependent methylation in the brain of patients with this disorder. S-Adenosylmethionine concentrations were measured in postmortem brain of 11 patients with Alzheimer's disease. We found decreased levels of S-adenosylmethionine (-67 to -85%) and its demethylated product S-adenosylhomocysteine (-56 to -79%) in all brain areas examined (cerebral cortical subdivisions, hippocampus, and putamen) as compared with matched controls (n = 14). S-Adenosylmethionine and S-adenosylhomocysteine levels were normal in occipital cortex of patients with idiopathic Parkinson's disease (n = 10), suggesting that the decreased S-adenosylmethionine levels in Alzheimer's disease are not simply a consequence of a chronic, neurodegenerative condition. Reduced S-adenosylmethionine levels could be due to excessive utilization in polyamine biosynthesis. The severe reduction in levels of this essential biochemical substrate would be expected to compromise seriously metabolism and brain function in patients with Alzheimer's disease and may provide the basis for the observations of improved cognition in some Alzheimer's patients following S-adenosylmethionine therapy.

ACTIVITY OF S-ADENOSYLMETHIONINE DECARBOXYLASE, A KEY REGULATORY ENZYME IN POLYAMINE BIOSYNTHESIS, IS INCREASED IN EPILEPTOGENIC HUMAN CORTEX

Morrison LD; Sherwin AL; Carmant L; Kish SJ
Human Neurochemical Pathology Laboratory, Clarke Institute of Psychiatry, Toronto, Ontario
Arch Neurol (UNITED STATES) Jun 1994, 51 (6) p581-4,

OBJECTIVE: We measured the activity of S-adenosylmethionine decarboxylase, a key regulatory enzyme of polyamine biosynthesis, in the temporal cortex of patients with epilepsy.

DESIGN: Cortical surgical specimens were obtained following anterior temporal lobe resection for intractable epilepsy. Enzyme activity was compared in nonpileptogenic (n = 16) and epileptogenic (spontaneously discharging; n = 19) regions.

RESULTS: Mean enzyme activity was increased by 44% in samples from epileptogenic cortex compared with samples from nonpileptic regions. The S-adenosylmethionine decarboxylase activity in regions of focal epileptogenic discharges was also

increased in five patients compared with paired samples from the nonepileptogenic portion of the same gyrus (+55%).

CONCLUSIONS: Elevated activity of S-adenosylmethionine decarboxylase in regions of active epileptogenic cortical discharges suggests that a disturbance of the polyamine system may be involved in the maintenance of hypersynchronous discharges, perhaps through a modulatory action at the excitatory N-methyl-D-aspartate-preferring glutamate receptor.

BRAIN S-ADENOSYLMETHIONINE DECARBOXYLASE ACTIVITY IS INCREASED IN ALZHEIMER'S DISEASE

Morrison LD; Bergeron C; Kish SJ

Human Neurochemical Pathology Laboratory, Clarke Institute Of Psychiatry, Toronto, Ont., Canada

Neurosci Lett (NETHERLANDS) May 14 1993, 154 (1-2) p141-4,

We measured the activity of S-adenosylmethionine decarboxylase (SAMDC), a key regulatory enzyme of polyamine biosynthesis, in autopsied brain from 13 patients with Alzheimer's Disease (AD). As compared with the controls, mean enzyme activity was increased by 37-96% in all seven examined brain regions with statistically significant increases in temporal cortex (+96%), frontal cortex (+69%) and hippocampus (+90%). The elevated SAMDC may have occurred as part of a generalized polyamine response to brain injury, which has been previously described in experimental animal conditions. Above-normal SAMDC activity implies increased levels/metabolism of spermidine and spermine, two polyamines which are involved in neuronal regeneration, growth factor production, and activation of excitatory N-methyl-D-aspartate preferring glutamate receptors. Our data suggest the involvement of the polyamine system in the brain reparative and/or pathogenetic mechanisms of AD.

EFFECT OF METHIONINE LOADING ON 5-METHYLTETRAHYDROFOLATE, S-ADENOSYLMETHIONINE AND S-ADENOSYLMETHIONINE IN PLASMA OF HEALTHY HUMANS

Loehrer FM; Haefeli WE; Angst CP; Browne G; Frick G; Fowler B

Metabolic Unit, University Children's Hospital Basel, Switzerland

Clin Sci (Colch) (ENGLAND) Jul 1996, 91 (1) p79-86,

1. Elevated plasma homocysteine concentration, either in the fasting state or after methionine loading, is an independent risk factor for vascular disease in man. Methionine loading has been used to investigate impaired methionine metabolism, especially of the trans-sulphuration pathway, but most studies have focused on changes in homocysteine.
2. Investigated the effect of methionine excess on total plasma homocysteine, 5-methyltetrahydrofolate (which is the active form of folate in the remethylation of homocysteine to methionine), S-adenosyl-methionine (the first metabolite of methionine) and S-adenosylmethionine (the demethylated product of S-adenosylmethionine) over 24h in 12 healthy subjects.
3. As well as the expected increase in homocysteine (from 8.0 +/- 1.3 to 32.6 +/- 10.3 $\mu\text{mol/l}$, mean +/- SD, P 0.001), S-adenosylmethionine showed a significant transient increase (from 37.9 +/- 25.0 to 240.3 +/- 109.2 nmol/l, P 0.001), which correlated well with homocysteine ($r^2 = 0.92$, P 0.001). 5-Methyltetrahydrofolate values decreased significantly (from 23.2 +/- 7.2 to 13.1 +/- 2.9 nmol/l, P 0.01), and gradually returned to baseline levels after 24h. No significant change over the time of measurement was found for S-adenosylhomocysteine.
4. The sequence of metabolic changes observed in this study strongly suggests that a change in either homocysteine or S-adenosylmethionine may cause a reduction in 5-methyltetrahydrofolate. This must be considered in evaluating the relationship between folate and homocysteine in vascular disease. The metabolic relationships illustrated in this study should be evaluated in the search for pathogenetic mechanisms of mild hyperhomocysteinaemia and vascular disease.

LOW WHOLE-BLOOD S-ADENOSYLMETHIONINE AND CORRELATION BETWEEN 5-METHYLTETRAHYDROFOLATE AND HOMOCYSTEINE IN CORONARY ARTERY DISEASE

Loehrer FM; Angst CP; Haefeli WE; Jordan PP; Ritz R; Fowler B

Metabolic Unit, University Children's Hospital, Basel, Switzerland

Arterioscler Thromb Vasc Biol (U. S.) Jun 1996, 16 (6) p727-33,

Mild elevation of plasma homocysteine is an independent risk factor for vascular disease. We studied the role of 5-methyltetrahydrofolate (5-MTHF), the folate form directly involved in homocysteine metabolism, in contrast to previous studies, which used total folate measurements, in 70 coronary artery disease (CAD) patients and control subjects. We also measured S-adenosylmethionine (SAM), which controls the activity of critical enzymes of homocysteine metabolism. Fasting plasma total homocysteine was elevated ($> 12.4 \mu\text{mol/L}$ for women, $> 13.3 \mu\text{mol/L}$ for men) in 17% of patients, in accordance with earlier studies. These patients showed lower 5-MTHF ($12.4 \pm 1.0 \mu\text{mol/L}$, mean +/- SD) than control subjects (24.2 ± 15.0 , P .001), and there was a clear correlation (multiple linear regression analysis: P = .002) of this relevant form of folate with homocysteine. However, 37% of the normohomocysteinemic patients also revealed similarly low 5-MTHF levels, suggesting that a decrease of 5-MTHF does not necessarily cause hyperhomocysteinemia. SAM was significantly decreased in patients ($1.4 \pm 0.4 \mu\text{mol/L}$) compared with control subjects (1.8 ± 0.3 , P .001) but was not correlated to homocysteine or 5-MTHF. The correlation between

homocysteine and 5-MTHF that was found in CAD patients but not in control subjects confirms the direct relationship between these compounds in vivo. The new finding of low SAM in patients demands further studies, since it might indicate that low levels pose risk and that SAM might be a protective factor against the development of CAD.

A PROSPECTIVE STUDY OF PLASMA HOMOCYST(E)INE AND RISK OF ISCHEMIC STROKE

Verhoef P; Hennekens CH; Malinow MR; Kok FJ; Willett WC; Stampfer MJ
Department of Epidemiology and Public Health, Agricultural University, Wageningen, Netherlands
Stroke (UNITED STATES) Oct 1994, 25 (10) p1924-30,

BACKGROUND AND PURPOSE: Several studies have reported elevated circulating homocyst(e)ine levels in subjects with cerebral atherosclerosis. We assessed prospectively whether high plasma levels of homocyst(e)ine affect risk of ischemic stroke and evaluated whether high blood pressure modifies any such effect.

METHODS: The study sample was drawn from the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in 22,071 US male physicians. A total of 14,916 subjects 40 to 84 years old with no prior history of stroke, transient ischemic attack, or myocardial infarction provided blood samples at baseline and were followed for 5 years, with 99.7% morbidity and 100% mortality follow-up. Using a nested case-control design, we assayed homocyst(e)ine in samples from 109 subjects who subsequently developed ischemic stroke and 427 control subjects.

RESULTS: The mean plasma concentration of homocyst(e)ine was slightly higher in subjects with stroke (11.1 +/- 4.0 [+/- SD] nmol/mL) than in control subjects (10.6 +/- 3.4 nmol/mL), but the difference was not statistically significant (P = .12). The crude odds ratio of ischemic stroke for subjects in the upper 20% (> 12.7 nmol/mL) compared with those in the bottom 80% of homocyst(e)ine levels was 1.4 (95% confidence interval, 0.8 to 2.2). The odds ratio was 1.2 (95% confidence interval, 0.7 to 2.0) after controlling for several risk factors and other potential confounders. In subgroup analyses, elevated homocyst(e)ine levels appeared to be more strongly predictive of ischemic stroke in normotensive subjects and in men 60 years or younger. Although not statistically significant, in these subgroups increases in risks of 100% and 70%, respectively, were observed for men in the upper 20% of homocyst(e)ine values.

CONCLUSIONS: In this study, the data were compatible with a small but nonsignificant association between elevated plasma homocyst(e)ine and risk of ischemic stroke. However, since the sample size is small and the confidence intervals are wide, either no association or a moderate increase in risk cannot be excluded, particularly in subgroups otherwise at low risk, eg, younger men and those with normal blood pressure.

A PROSPECTIVE STUDY OF PLASMA HOMOCYST(E)INE AND RISK OF MYOCARDIAL INFARCTION IN US PHYSICIANS

Stampfer MJ; Malinow MR; Willett WC; Newcomer LM; Upson B; Ullmann D; Tishler PV; Hennekens CH
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA
JAMA (UNITED STATES) Aug 19 1992, 268 (7) p877-81,

OBJECTIVE-To assess prospectively the risk of coronary heart disease associated with elevated plasma levels of homocyst(e)ine.

DESIGN-Nested case-control study using prospectively collected blood samples.

SETTING-Participants in the Physicians' Health Study.

PARTICIPANTS-A total of 14,916 male physicians, aged 40 to 84 years, with no prior myocardial infarction (MI) or stroke provided plasma samples at baseline and were followed up for 5 years. Samples from 271 men who subsequently developed MI were analyzed for homocyst(e)ine levels together with paired controls, matched by age and smoking.

MAIN OUTCOME MEASURE-Acute MI or death due to coronary disease.

RESULTS-Levels of homocyst(e)ine were higher in cases than in controls (11.1 +/- 4.0 [SD] vs 10.5 +/- 2.8 nmol/mL; P = .03). The difference was attributable to an excess of high values among men who later had MIs. The relative risk for the highest 5% vs the bottom 90% of homocyst(e)ine levels was 3.1 (95% confidence interval, 1.4 to 6.9; P = .005). After additional adjustment for diabetes, hypertension, aspirin assignment, Quetelet's Index, and total/high-density lipoprotein cholesterol, this relative risk was 3.4 (95% confidence interval, 1.3 to 8.8) (P = .01). Thirteen controls and 31 cases (11%) had values above the 95th percentile of the controls.

CONCLUSIONS-Moderately high levels of plasma homocyst(e)ine are associated with subsequent risk of MI independent of other coronary risk factors. Because high levels can often be easily treated with vitamin supplements, homocyst(e)ine may be an independent, modifiable risk factor.

ALTERATIONS TO PLASMA MELATONIN AND CORTISOL AFTER EVENING ALPRAZOLAM ADMINISTRATION IN HUMANS

McIntyre IM; Norman TR; Burrows GD; Armstrong SM
Victorian Institute of Forensic Pathology, Monash University, South Melbourne, Australia
Chronobiol Int (UNITED STATES) Jun 1993, 10 (3) p205-13,

Healthy volunteers were given a 2-mg dose of alprazolam at 21:00 h and hourly blood samples were collected until 08:00 h the following morning. A control night of hourly blood sampling was undertaken 7 days before. Plasma was analyzed for melatonin, cortisol, and alprazolam concentrations. Melatonin concentrations were significantly suppressed by alprazolam at 23:00, midnight, 01:00, 06:00, and 07:00 h. A trend toward suppression was evident from 02:00 to 05:00 h. Cortisol concentrations were also suppressed by alprazolam at several times throughout the night (01:00-04:00 h). Plasma alprazolam levels showed a peak at 3 h and remained relatively high 19-20 h after the dose. The significance of melatonin suppression by alprazolam is discussed in terms of benzodiazepine binding sites and GABA-minergic transmission in the human pineal gland, suprachiasmatic nuclei, and retina. Plasma cortisol suppression has been reported for other benzodiazepine drugs, but conflicting data exist for alprazolam. The present results do not support the proposed inhibitory effect of melatonin on the hypothalamic-pituitary-adrenal (HPA)-axis. It is suggested that there is no simple direct relationship between melatonin and the HPA axis in humans.

EFFECT OF AGEING ON MELATONIN SYNTHESIS INDUCED BY 5-HYDROXYTRYPTOPHAN AND CONSTANT LIGHT IN RATS

McIntyre IM; Oxenkrug GF
Department of Psychiatry, University of Melbourne, Vic., Australia
Prog Neuropsychopharmacol Biol Psychiatry (ENGLAND) 1991, 15 (4) p561-6,

1. This paper describes the effect of the serotonin precursor 5-hydroxytryptophan (5-HTP) on pineal melatonin synthesis in young and old rats.
2. 5-HTP itself increased pineal melatonin levels in old rats but did not change melatonin concentrations in young rats kept under 12 hr/12 hr light/dark conditions.
3. After continuous exposure to light for 72 hrs, 5-HTP induced a significant increase in melatonin levels in young rats but did not change the 5-HTP effect on melatonin in old animals.
4. These results are discussed in consideration of previous reports of altered beta-receptor up-regulation by light in old animals, and suggest that the age-related decrease in melatonin synthesis is not entirely related to changes of the enzymatic machinery for melatonin synthesis. Meta-analysis, clinical trials, and transferability of research results into practice.

THE CASE OF CHOLESTEROL-LOWERING INTERVENTIONS IN THE SECONDARY PREVENTION OF CORONARY HEART DISEASE

Marchioli R; Marfisi RM; Carinci F; Tognoni G
Department of Clinical Pharmacology and Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri-Consortio Mario Negri Sud, Santa Maria Imbaro, Italy
Arch Intern Med (U. S.) Jun 10 1996, 156 (11) p1158-72,

OBJECTIVE: To evaluate, in the comprehensive scenario of "evidence-based" medicine, the transferability of the results of published randomized clinical trials and meta-analyses on cholesterol-lowering interventions to clinical practice.

METHOD: Overview of randomized clinical trials on cholesterol-lowering interventions in the secondary prevention of coronary heart disease.

RESULTS: The present overview on secondary prevention of coronary heart disease included 34 trials with cholesterol-lowering interventions in 24968 individuals. There was a 12.5% mortality in the group that was allocated active intervention and a 17.2% mortality in the control group (risk reduction, 13%; 95% confidence interval, -19% to -6%). Coronary and cardiovascular odds of deaths were significantly reduced. No clear association was found between noncoronary mortality and cholesterol-lowering interventions. Baseline total cholesterol levels had no clear influence on total mortality. Intermediate (10%-20%) and high (> 20%) total cholesterol reductions were associated with similar reductions in the odds of death (-23% and -30%, respectively). No conclusion could be reached for patients who were less represented in the studies (ie, women and elderly persons). Patients with more complicated baseline clinical conditions (eg, congestive heart failure) had little nonsignificant benefit from cholesterol-

lowering interventions.

CONCLUSIONS: The effect of cholesterol-lowering interventions at least in the secondary prevention of coronary heart disease can be considered as established, but the transferability of such results to real-life patients remains the critical, unanswered question. (163 Refs.)

EFFECTS OF DIAZEPAM ADMINISTRATION ON MELATONIN SYNTHESIS IN THE RAT PINEAL GLAND IN VIVO

Wakabayashi H; Shimada K; Satoh T
Department of Analytical Chemistry,
Niigata College of Pharmacy, Japan
Chem Pharm Bull (Tokyo) (JAPAN) Oct 1991, 39 (10) p2674-6,

The effect of diazepam (DZP) on melatonin synthesis in rat pineal gland was investigated in vivo. Subcutaneous injection of DZP (3 mg/kg) 1 h before the start of darkness significantly suppressed nocturnal elevations of pineal N-acetylserotonin (NAS) and melatonin contents in rats, and caused a 2-h delay in reaching the maximum melatonin level in the dark phase. DZP treatment also markedly suppressed the dark-induced increase of pineal N-acetyltransferase activity, which catalyzes the rate-limiting step in melatonin synthesis, but had no effect on hydroxyindole-O-methyltransferase activity, which catalyzes the final step of melatonin formation. Pineal norepinephrine and dopamine contents, in contrast, were not altered by DZP injection. The distribution rate of DZP to the brain reached the highest level 30 min after a single injection, while that to the pineal gland was observed 5 h later (i.e., 4 h after the start of darkness). It is clear that the inhibitory effect of DZP on melatonin synthesis in rat pineal gland appears concomitantly with the increase in the distribution volume of DZP into this gland. These results suggest that the inhibitory effect of DZP on melatonin synthesis results from the drug's direct action on the rat pineal gland.

NYCTOHEMERAL RHYTHM IN THE LEVELS OF S-ADENOSYLMETHIONINE IN THE RAT PINEAL GLAND AND ITS RELATIONSHIP TO MELATONIN BIOSYNTHESIS

Sitaram BR; Sitaram M; Traut M; Chapman CB
School of Pharmaceutics, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia
J Neurochem (UNITED STATES) Oct 1995, 65 (4) p1887-94,

Liquid chromatographic techniques that permit the simultaneous analysis of S-adenosylmethionine, melatonin, and its intermediary metabolites N-acetyl-5-hydroxytryptamine and 5-hydroxytryptamine within individual pineal glands have been developed. S-Adenosylmethionine has been shown to undergo a marked nyctohemeral rhythm in the pineal gland of the rat, with maximal levels occurring during the light period and minimal levels during the dark period. Detailed studies of the temporal relationships between the levels of S-adenosylmethionine and those of melatonin and its intermediary metabolites suggest that an association exists between the levels of S-adenosylmethionine and the status of the biosynthesis of melatonin. Exposure of animals to continuous light and the administration of the beta-adrenoreceptor antagonist propranolol were both found to inhibit the induction of melatonin synthesis and prevent the reduction in the levels of S-adenosylmethionine during the dark period. As a corollary the induction of melatonin biosynthesis following the administration of the beta-adrenoreceptor agonist isoproterenol during the light period was accompanied by a marked decrease in the levels of S-adenosylmethionine in the pineal gland. The significance of the link between the nyctohemeral rhythms in the levels of S-adenosylmethionine and the biosynthesis of melatonin in the pineal gland is discussed in the context of the therapeutic efficacy of S-adenosylmethionine as an antidepressant.

MELATONIN SECRETION RELATED TO SIDE-EFFECTS OF BETA-BLOCKERS FROM THE CENTRAL NERVOUS SYSTEM

Brismar K; Hylander B; Eliasson K; Rossner S; Wetterberg L
Department of Endocrinology, Karolinska Hospital, Sweden
Acta Med Scand (SWEDEN) 1988, 223 (6) p525-30,

In two studies of hypertensive patients the relationship between beta-blocker-induced CNS side-effects and the nightly urinary secretion of melatonin was analysed. In one group (n = 10) placebo, atenolol (mean dose 86 mg/day) or propranolol (mean dose 305 mg/day) were given in a double-blind, randomised design. In the other (n = 13) 100-400 mg metoprolol was given daily (mean dose 197 mg). After 4 weeks of treatment all beta-blockers reduced melatonin excretion, but the effect was significant only for metoprolol. Sleep disturbance records revealed more disturbed nights in the metoprolol group compared with the propranolol and the atenolol groups, even when the difference in age between the groups was controlled for. In the metoprolol group a significant relationship (p less than 0.05) was found between the fall in melatonin and the percentage of disturbed nights. Severe CNS side-effects, such as nightmares, occurred only in patients treated with metoprolol (21%), which in all cases were accompanied by low levels of melatonin. Our data suggest that the CNS side-effects during beta-blockade are related to a reduction of melatonin levels.

S-ADENOSYL-L-METHIONINE (SAME) AS ANTIDEPRESSANT: META-ANALYSIS OF CLINICAL STUDIES

Bressa GM Department of Psychiatry, University Cattolica Sacro Cuore School of Medicine, Rome, Italy
Acta Neurol Scand Suppl (DENMARK) 1994, 154 p7-14,

INTRODUCTION-S-adenosyl-L-methionine (SAME) is a naturally-occurring substance which is a major source of methyl groups in the brain.

MATERIAL AND METHODS-We conducted a meta-analysis of the studies on SAME to assess the efficacy of this compound in the treatment of depression compared with placebo and standard tricyclic antidepressants.

RESULTS-Our meta-analysis showed a greater response rate with SAME when compared with placebo, with a global effect size ranging from 17% to 38% depending on the definition of response, and an antidepressant effect comparable with that of standard tricyclic antidepressants.

CONCLUSION-The efficacy of SAME in treating depressive syndromes and disorders is superior with that of placebo and comparable to that of standard tricyclic antidepressants. Since SAME is a naturally occurring compound with relatively few side-effects, it is a potentially important treatment for depression.

S-ADENOSYLMETHIONINE BLOOD LEVELS IN MAJOR DEPRESSION: CHANGES WITH DRUG TREATMENT

Bell KM; Potkin SG; Carreon D; Plon L
University of California, Irvine Medical Center, Orange 92668
Acta Neurol Scand Suppl (DENMARK) 1994, 154 p15-8,

INTRODUCTION-The relationship between plasma levels of S-adenosylmethionine (SAME), an endogenous methyl donor, and clinical response were studied in patients with a DSM-III-R diagnosis of major depression.

MATERIAL AND METHODS-A double-blind randomized protocol comparing oral SAME with oral desipramine, involving a total of 26 patients, was employed.

RESULTS-At the end of the 4-week trial, 62% of the patients treated with SAME and 50% of the patients treated with desipramine had significantly improved. Regardless of the type of treatment, patients with a 50% decrease in their Hamilton Depression Scale (HAM-D) score showed a significant increase in plasma SAME concentration.

CONCLUSION-The significant correlation between plasma SAME levels and the degree of clinical improvement in depressed patients regardless of the type of treatment suggests that SAME may play an important role in regulating mood.

EFFICACY OF S-ADENOSYL-L-METHIONINE IN SPEEDING THE ONSET OF ACTION OF IMIPRAMINE

Berlanga C; Ortega-Soto HA; Ontiveros M; Senties H
Special Studies Clinic, Mexican Institute of Psychiatry, Tlalpan
Psychiatry Res (IRELAND) Dec 1992, 44 (3) p257-62,

A double-blind clinical trial was carried out to evaluate the efficacy of S-adenosyl-L-methionine (SAME) in speeding the onset of action of imipramine (IMI). SAME is a naturally occurring substance that has been shown to possess antidepressant activity with a rapid mode of onset and minimal side effects. Sixty-three outpatients with moderate to severe depression were included in the study. After an initial 1-week placebo period, only 40 patients entered the active treatment phase. During the first 2 weeks of the trial, half of these patients received 200 mg/day of SAME intramuscularly, while the other half received placebo. Simultaneously, oral IMI was administered to all patients at a fixed dose of 150 mg/day. The onset of clinical response was determined by evaluating patients every second day. By the end of week 2, the parenteral treatment was suppressed and IMI was adjusted according to individual needs. Depressive symptoms decreased earlier in the patients who were receiving the SAME-IMI combination than in those who were receiving the placebo-IMI combination.

ORAL S-ADENOSYLMETHIONINE IN PRIMARY FIBROMYALGIA-DOUBLE-BLIND CLINICAL EVALUATION

Jacobsen S; Danneskiold-Samsøe B; Andersen RB
Department of Rheumatology, Frederiksberg Hospital, Copenhagen, DK
Scand J Rheumatol (SWEDEN) 1991, 20 (4) p294-302,

S-adenosylmethionine is a relatively new anti-inflammatory drug with analgesic and anti-depressant effects. Efficacy of 800 mg orally administered S-adenosylmethionine daily versus placebo for six weeks was investigated in 44 patients with primary fibromyalgia in double-blind settings. Tender point score, isokinetic muscle strength, disease activity, subjective symptoms (visual analog scale), mood parameters and side effects were evaluated. Improvements were seen for clinical disease activity ($P = 0.04$), pain experienced during the last week ($P = 0.002$), fatigue ($P = 0.02$), morning stiffness ($P = 0.03$) and mood evaluated by Face Scale ($P = 0.006$) in the actively treated group compared to placebo. The tender point score, isokinetic muscle strength, mood evaluated by Beck Depression Inventory and side effects did not differ in the two treatment groups. S-adenosylmethionine has some beneficial effects on primary fibromyalgia and could be an important option in the treatment hereof.

CEREBROSPINAL FLUID S-ADENOSYLMETHIONINE IN DEPRESSION AND DEMENTIA:

Effects of treatment with parenteral and oral S-adenosylmethionine
Bottiglieri T; Godfrey P; Flynn T; Carney MW; Toone BK;
Department of Neurology, King's College Hospital, London UK
J Neurol Neurosurg Psychiatry (ENGLAND) Dec 1990, 53 (12) p1096-8,

Cerebrospinal fluid (CSF) S-adenosylmethionine (SAM) levels were significantly lower in severely depressed patients than in a neurological control group. The administration of SAM either intravenously or orally is associated with a significant rise of CSF SAM, indicating that it crosses the blood-brain barrier in humans. These observations provide a rational basis for the antidepressant effect of SAM, which has been confirmed in several countries. CSF SAM levels were low in a group of patients with Alzheimer's dementia suggesting a possible disturbance of methylation in such patients and the need for trials of SAM treatment.

THE ANTIDEPRESSANT POTENTIAL OF ORAL S-ADENOSYL-L-METHIONINE

Rosenbaum JF; Fava M; Falk WE; Pollack MH; Cohen LS; Cohen BM; Zubenko GS
Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston 02114
Acta Psychiatr Scand (DENMARK) May 1990, 81 (5) p432-6,

S-adenosyl-L-methionine (SAME), a naturally occurring brain metabolite, has previously been found to be effective and tolerated well in parenteral form as a treatment of major depression. To explore the antidepressant potential of oral SAME, we conducted an open trial in 20 outpatients with major depression, including those with ($n = 9$) and without ($n = 11$) prior history of antidepressant nonresponse. The group as a whole significantly improved with oral SAME: 7 of 11 non-treatment-resistant and 2 of 9 treatment-resistant patients experienced full antidepressant response. Side effects were mild and transient.

ORAL S-ADENOSYLMETHIONINE IN DEPRESSION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Kagan BL; Sultzer DL; Rosenlicht N; Gerner RH
Department of Psychiatry, West Los Angeles VA Medical Center, CA
Am J Psychiatry (UNITED STATES) May 1990, 147 (5) p591-5,

Methylation has been implicated in the etiology of psychiatric illness. Parenteral S-adenosylmethionine, a methyl group donor, has been shown to be an effective antidepressant. The authors studied the antidepressant effect of oral S-adenosylmethionine in a randomized, double-blind, placebo-controlled trial for 15 inpatients with major depression. The results suggest that oral S-adenosylmethionine is a safe, effective antidepressant with few side effects and a rapid onset of action. S-Adenosylmethionine induced mania in a patient with no history of mania. S-Adenosylmethionine may be useful for patients who cannot tolerate tricyclic anti-depressants. These findings support a role for methylation in the pathophysiology of depression.

REVIEW ARTICLE: S-ADENOSYL-L-METHIONINE-A NEW THERAPEUTIC AGENT IN LIVER DISEASE?

Osman E; Owen JS; Burroughs AK
University Dept of Medicine, Royal Free Hospital, UK
Aliment Pharmacol Ther (ENGLAND) Feb 1993, 7 (1) p21-8,

The established biochemical effects of exogenous S-Adenosyl-L-Methionine (SAME) are diverse and are still being explored in liver disease. Putative therapeutic effects could be exerted via different mechanisms. The established deficiency of SAME synthetase in cirrhosis could be bypassed by exogenous SAME, leading to increased levels of sulphur-containing amino acids and glutathione which would protect against oxidant stress and drug-induced hepatotoxicity (for example, paracetamol). Furthermore SAME could act by improving membrane fluidity, and thus potentially improve or restore the function of receptors, enzymes and transporters in the cell surface. Membrane fluidity is known to be affected by alterations in cell membrane lipid composition in chronic liver disease. Very few therapeutic agents are effective for the symptomatic or specific treatment of

chronic liver disease. SAmE has established biochemical and biophysical effects which in pilot studies ameliorate symptoms and biochemical parameters of cholestasis. Moreover, abnormalities in liver function tests (including transaminase values) also improve. Before SAmE can be considered as an established therapy for patients with hepatic disease, long-term controlled clinical trials of SAmE are needed to assess the benefit for patients' symptoms, well being, histological changes and progression of liver disease. (54 Refs.)

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