

LE Magazine May 2001

## ABSTRACTS

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#### Mercury Detoxification

Purging the body of excess mercury is a complex process that should be overseen by a physician with specialized expertise in mercury detoxification. In this issue, we provide a list of dietary supplements, drugs and blood-urine tests that doctors use to facilitate mercury detoxification. What follows are additional steps that should be followed (under a physician's supervision) for complete mercury detoxification.

#### Diet

Avoid all sugar and milk, limit all processed foods and most grains, especially wheat.

A high protein diet will provide sulfur bearing amino acids to greatly facilitate detoxification. Do not attempt to fast during DMPS mercury detoxification. If you are a vegetarian you will be at high risk for complications from DMPS unless you have a large amount of protein.

To add the right form of protein, whey is suggested to boost glutathione and provide branched chain amino acids. Two large tablespoons of a highly concentrated whey isolate are used per drink to be taken once a day for the first week and then twice a day for the week prior to DMPS chelation.

Note: Autistic children can't use this product, as it contains casein. They can use pure branched chain amino acids. You can start with one capsule twice daily and mix with food. Work up to two capsules twice a day for the week prior to DMPS chelation.

#### Beneficial bacteria

Take four capsules a day of a high potency/ high quality strain of beneficial bacteria such as that found in the Life Flora product made by Source Naturals. It is vital to have an optimized bowel flora for detoxification.

#### Digestive system

Because mercury is also eliminated via the fecal route it is important that you have two to three bowel movements per day. Freshly ground flax seed several teaspoons per day will facilitate intestinal movement and also contribute some healthy essential fatty acids. High dose vitamin C and mineral salts (magnesium and potassium) on an empty stomach will also stimulate peristalsis to induce multiple bowel movements throughout the day.

#### Check the endocrine system

Mercury is toxic to the endocrine system with high affinity for pituitary and thyroid glands. Make certain that your thyroid status has been checked using Free T3, Free T4, TSH blood tests as well as axillary basal metabolic morning temperatures before commencing detoxification. Conservative estimates are that more than 60 million Americans have a thyroid hormone deficiency. Many of these hypothyroid patients have been told by traditional testing methods and traditional physicians that their thyroid function is normal. Mercury almost always affects the thyroid!

#### Unload the connective tissue with chlorella or chitosan

Chlorella and chitosan are an important part of the detoxification program, as approximately 90% of the mercury in our bodies is eliminated through the stool. Chlorella is an algae and, unlike chitosan, has high protein levels of chlorophyll and other nutrients that can be used for nourishment.

The chlorella powder is the most cost effective approach but some people will prefer the tablets or capsules for convenience. A

simple way to dissolve the powder is to place it in a container with a lid partially filled with water. Then tighten the lid and shake to dissolve and drink the solution.

Caution: About 30% of people can't tolerate chlorella. This may be due to optimized function of the enzyme cellulase. If you are unable to tolerate this it would be wise to consider adding an enzyme with cellulase in it to help digest the chlorella.

Dose: One can start out with one quarter of a teaspoon of the powder (one 500 mg tablet) once a day initially to confirm that there is no hypersensitivity present. Work up slowly over one to two weeks to a dose of one teaspoon (ten tablets or capsules) per day. Once you tolerate this dose you are able to use it to bind the mercury. Use this dose starting two days prior to your chelation and for one day afterwards. The chlorella will thoroughly coat your intestine and bind like a sponge to any mercury that the DMPS liberates into the gut.

The above dose is based on a 150 pound adult. If you are using the program for children reduce the dose proportionately. (So a 30 pound child would have 30/150 or 1/5 (20%) of the dose).

Caution: If at any time one develops nausea or starts "burping up" the chlorella taste then the chlorella should be stopped immediately, as a food sensitivity is developing that will only worsen if you continue taking it. If this happens you should switch to ProChitosan. This binds similarly to mercury. Its dose is dependent on your bowel movements.

If you have one bowel movement a day or less you should start two days prior to the DMPS. If you have two or more bowel movements you can start 24 hours prior to the DMPS. Stay on it for 24 hours after the DMPS. So you will be on it either two or three days. The dose is two capsules three times a day. Be sure to drink it with plenty of water and increase magnesium if constipation develops.

Porphrazyme from Biotics Research is another alternative to chlorella that many clinicians have had success with in mercury detoxification.

#### Sulfur supplement

It would be wise to start on garlic regularly to enhance sulfur stores. You can either use a high-allylicin garlic supplement or get it in three cloves per day. Decrease the dose if your odor becomes socially offensive.

MSM (methylsulfonyl methane) is a form of sulfur that will help your body to remove the mercury. The initial dose is one capsule twice a day. Increase by one capsule a day until you are at three capsules twice a day. If you have root canals and are chronically sick you may want to increase to five capsules three times a day.

#### Cilantro

Cilantro will help mobilize mercury out of the tissue so the DMPS can attach to it and allow it to be excreted from the body. The best form of cilantro is a tincture.

The dose is one dropper applied on the wrists and rubbed in twice a day for the two weeks preceding the DMPS IV. It is used the morning prior to the DMPS chelation but can be stopped for the following two weeks. The tincture is also particularly useful for any joint pain and could be rubbed on the joint that is hurting as an alternative.

You can also augment the tincture by using the herb. It is not as potent, but it will certainly add to the program. However, like chlorella, many people are sensitive to oral cilantro. So, if you develop any nausea or discomfort after eating cilantro do not use it orally.

#### Mineral replacement

It is important to have a generally healthy mineral base. When you are deficient in magnesium, sodium, zinc and other minerals, the body does not let go of toxic metals like mercury very easily.

Selenium and zinc are particularly important trace minerals in mercury detoxification and should be used for most people.

#### Monitor your mineral dosing

It will be very important for your physician to monitor your mineral levels during the detoxification program. This should be done initially and at least every 6 to 12 weeks. High dose vitamins and minerals should be administered Intravenously (IV) after each DMPS treatment and as needed. It is difficult if not impossible to provide adequate mineral replacements solely from oral supplementation after receiving DMPS or DMSA.

## Digestion and gall bladder support

Liver and gallbladder congestion are major issues in states of toxicity. To insure that your gallbladder bile flow is functional, take four tablets of Digest RC right before any fatty meal. This supplement provides a proprietary artichoke and black radish extract that stimulates bile acid flow from the gall bladder. Digestive enzymes should also be used before or right after each meal.

Other ways of stimulating bile flow include using taurine and butyric acid. Butyrex is a popular butyric acid supplement. The dose of the Butyrex initially is 1/8 to 1/4 of a capsule. Gradually increase the dose to five capsules three times daily. The Butyrex has a offensive odor that is lessened by keeping it in the freezer. Additionally inserting the powder in applesauce, raw honey or elderberry cough syrup may improve compliance.

Your ability to clear toxins will be impaired if you do not have proper fats to support digestive function. Your diet should contain adequate fat from unprocessed pure oils. Omega Nutrition, Flora or Arrowhead Mills offer sunflower, safflower and sesame supplements. Alternately, be sure your diet include fats naturally found in foods: seeds, nuts, avocado, free range organic poultry, eggs or meats.

## Antioxidants

Vitamin C and E. Take 5,000 to 10,000 total milligrams of vitamin C per day along with 400 to 800 IU of vitamin E.

It is very important to take 2000 units (typically five of the 400 unit capsules) of vitamin E the day of and the day after the DMPS injection, as this will decrease the side effects of the detoxification reaction considerably. You can also take 1 to 2 grams of vitamin C immediately prior to the DMPS injection.

## Monthly DMPS injections, suppositories or transdermal

You should not have DMPS treatments if you still have amalgam fillings. If they have been removed the injections can be started by a trained and experienced physician as per protocol. Collection of the urine is then done to analyze how much mercury is being excreted. You must urinate completely prior to the DMPS injection.

A six hour urine test is then performed by the patient. The DMPS injections are generally given about six times or until the mercury level drops in accordance with the physician's protocol. Remember, the World Health Organization states there is no safe level of mercury in the human body.

## For pediatric patients

DMSA mercury detoxification is not recommended for pediatric patients. Since an IV is such a traumatic event for most children it is probably wise to use a rectal suppository version of DMPS.

Caution: It is very important to never receive DMPS nor EDTA chelation treatments when you still have mercury fillings in your mouth.

## DMPS alternative

Some people do not tolerate DMPS well. This is especially true for those who have damage in the central nervous system, such as those with MS or ALS or children with fragile brain architecture. If this is the case there are several options. PCA (peptid clathrating agent) spray can be used. The dose is four sprays under the tongue every day or every other day. One may use a dipeptide amino acid or mixed mineral succinates such as Champion Nutrition Muscle Nitro.

## A note of caution:

The doctors who provided this information on mercury detoxification (Charles Williamson, M.D. and Jordan Davis, M.D.) do not recommend any mercury detoxification procedures or mercury amalgam removal by any dentist, biologic, mercury free or otherwise or any other health care practitioner without first and foremost being under the direct care of a medical doctor who has been properly trained and has sufficient experience in the evaluation, diagnosis and treatment of mercury toxic patients. To do otherwise can often lead to serious metabolic and organ system dysfunction and failure.

## The environmental effects of dental amalgam.

Dental amalgam is one of the most commonly used materials in restorative dentistry. However, one of its major components, mercury, is of particular concern due to its potential adverse effects on humans and the environment. In this review, the

environmental impact of dental amalgam will be discussed, with particular reference to the effects attributed to its mercury component. Mercury commonly occurs in nature as sulfides and in a number of minerals. Globally, between 20,000 to 30,000 tons of mercury are discharged into the environment each year as a result of human activities. According to a recent German report, approximately 46% of the freshly triturated amalgam is inserted as new amalgam restorations and the rest is waste. Depending on the presence of an amalgam separating unit, some of the generated amalgam-contaminated sludge is discharged into the sewage system. Lost or extracted teeth with amalgam fillings and amalgam-contaminated waste, such as trituration capsules and cotton rolls are discharged with the solid waste and, in most instances, are incinerated. Use of disinfectants containing oxidizing substances in dental aspirator kits may contribute to remobilization of mercury and its subsequent release into the environment. Nevertheless, dental mercury contamination is only a small proportion of terrestrial mercury (3% to 4%), which is quite insignificant compared with industrial pollution and combustion of fossil fuels by vehicles. The environmental impact of dental mercury is mainly due to the poor management of dental amalgam waste. Proper collection of mercury-contaminated solid waste prevents the release of mercury vapour during combustion. In addition, the use of amalgam separating devices reduces the amount of amalgam-contaminated water released from dental clinics.

Aust Dent J 2000 Dec;45(4):246-9

Dental amalgam and mercury in dentistry.

Mercury in dentistry has re-emerged as a contentious issue in public health, predominantly because so many people are inadvertently exposed to mercury in order to obtain the benefits of dental amalgam fillings, and the risks remain difficult to interpret. This commentary aims to examine the issues involved in public policy assessment of the continued use of dental amalgam in dentistry. More than 30% of Australian adults are concerned about mercury from dental amalgam fillings but only a small percentage report having their amalgam fillings removed. The placement of dental fillings nearly halved between 1983 and 1997, but many millions of dental amalgam fillings exist in the Australian community. These fillings release mercury (mercury vapour or inorganic ions) at a low level (about 2-5 micrograms/day in an adult). Evidence on the health effect of dental amalgams comes from studies of the association between their presence and signs or symptoms of adverse effects or health changes after removal of dental amalgam fillings. More formal risk assessment studies focus on occupational exposure to mercury and health effects. Numerous methodological issues make their interpretation difficult but new research will continue to challenge policymakers. Policy will also reflect prudent and cautious approaches, encouraging minimization of exposure to mercury in potentially more sensitive population groups. Wider environmental concerns and decreasing tolerance of exposure to other mercury compounds (for example, methylmercury in seafoods) will ensure the use of mercury in dentistry remains an issue, necessitating dentists keep their patients informed of health risks and respect their choices.

Aust Dent J 2000 Dec;45(4):224-34

Relation between mercury concentrations in saliva, blood and urine in subjects with amalgam restorations.

The aim was to determine the relationship between mercury content of resting and stimulated saliva, and blood and urine. Eighty subjects participated; 40 of them attributed their self-reported complaints to dental amalgam (patients), the others were matched with respect to age, sex and amalgam restorations (controls). Serum, 24 hour urine, resting and chewing stimulated saliva were analyzed for mercury using the ASS-technique. Quality, number, surfaces and total area of amalgam fillings were recorded clinically and using study models. Median (range) mercury levels in serum were 0.67 (0.1-1.52) microgram/l for patients and 0.60 (0.1-1.3) for controls. In urine levels were found to be 0.77 (0.11-5.16) and 0.94 (0.17-3.01) microgram/g creatinine respectively. No significant differences were found between the groups. Resting saliva contained 2.97 (0.10-45.46) micrograms/l in patients and 3.69 (0.34-55.41) in controls (not significant). Chewing mobilized an additional amount of 16.78 (-6.97 to 149.78) micrograms/l in patients and 49.49 (-1.36 to 504.63) in controls ( $P < \text{or} = 0.01$ ). Only a weak correlation was found between mobilized mercury in saliva and serum ( $r = 0.27$ ;  $P < \text{or} = 0.05$ ) or urine ( $r = 0.47$ ;  $P < \text{or} = 0.001$ ). For resting saliva the respective values were  $r = 0.45$  ( $P < \text{or} = 0.001$ ) and  $r = 0.60$  ( $P < \text{or} = 0.001$ ). Saliva testing is not an appropriate measure for estimating the mercury burden derived from dental amalgam.

Clin Oral Investig 2000 Dec;4(4):206-11

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## ABSTRACTS

## Stroke/Cardiovascular Disease

## Incidence of silent stroke in the United States.

**Background:** Recent estimates of stroke incidence in the US range from 715,000 to 750,000 annually. These estimates, however, do not reflect silent infarcts and hemorrhages. Since population-based studies have found that prevalence of silent stroke is 10 to 20 times that of symptomatic, estimates of stroke incidence based solely on symptomatic events may substantially underestimate the annual burden of stroke. Silent strokes contribute to vascular dementia, gait impairment and other major adverse patient outcomes. **Methods:** Incidence of silent infarcts for different age strata were derived from two US population-based studies of the prevalence of silent infarct-like lesions on MRI, Atherosclerosis Risk In Communities and Cardiovascular Health Study. Prevalence observations in these studies and age-specific death rates from the US Census Bureau were inputted to calculate silent infarct incidence (method of Leske et al). Similarly, incidence rates of silent hemorrhage at differing ages were extrapolated from population-based prevalence observations employing MR GRE imaging in the Austrian Stroke Prevention Study. Age-specific incidence rates were projected onto age cohorts in the 1998 US population to calculate annual burden of silent stroke. **Results:** Derived incidence rates per 100,000 of silent infarct ranged from 6400 in the age 50 to 59 strata to 16400 at ages 75 to 79. Extrapolated incidence rates of silent hemorrhage ranged from 230 in the age 30 to 39 strata to 7360 at ages > 80. Incidence rates of both subclinical infarcts and hemorrhage increased exponentially with age. Overall estimated annual US occurrence of silent infarct was 9,039,000, and of silent hemorrhage 2,130,000. **Conclusion:** In 1998, nearly 12 million strokes occurred in the United States, of which 750,000 were symptomatic and over 11 million were subclinical. Among the silent strokes, 81% were infarcts and 19% hemorrhages. These findings demonstrate that the annual burden of stroke is substantially higher than suggested by estimates based solely on clinically manifest events, and suggest that greater research and clinical resources should be allocated to stroke prevention and treatment.

Stroke. 2000;32:363-b

## Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women.

**BACKGROUND:** C-reactive protein (CRP) predicts risk of myocardial infarction (MI) and stroke among apparently healthy men, but in women, virtually no data are available. **METHODS AND RESULTS:** CRP was measured in baseline blood samples from 122 apparently healthy participants in the Women's Health Study who subsequently suffered a first cardiovascular event and from 244 age- and smoking-matched control subjects who remained free of cardiovascular disease during a three year follow-up period. Women who developed cardiovascular events had higher baseline CRP levels than control subjects ( $P=0.0001$ ), such that those with the highest levels at baseline had a five-fold increase in risk of any vascular event ( $RR=4.8$ ; 95% CI, 2.3 to 10.1;  $P=0.0001$ ) and a seven-fold increase in risk of MI or stroke ( $RR=7.3$ ; 95% CI, 2.7 to 19.9;  $P=0.0001$ ). Risk estimates were independent of other risk factors, and prediction models that included CRP provided a better method to predict risk than models that excluded CRP (all  $P$  values  $<0.01$ ). In stratified analyses, CRP was a predictor among subgroups of women with low as well as high risk as defined by other cardiovascular risk factors. **CONCLUSIONS:** In these prospective data among women, CRP is a strong independent risk factor for cardiovascular disease that adds to the predictive value of risk models based on usual factors alone.

Circulation 1998 Aug 25;98(8):731-3

## Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke.

**BACKGROUND AND PURPOSE:** The prognostic influences of fibrinogen and C-reactive protein (CRP) levels and their relations in ischemic stroke have not been well described. The aim of this study was to investigate and compare the one year prognostic influences of fibrinogen and CRP levels on outcome in ischemic stroke. **METHODS:** Fibrinogen and CRP were determined within 24 hours after stroke and related to one year outcome in 128 patients with first-ever ischemic stroke. The Kaplan-Meier technique was applied in survival analysis. Multiple logistic regression analysis was used to evaluate the associations between risk factors and outcome. **RESULTS:** The probabilities of death or new vascular event were 21.1%, 27.9%, and 51.7% ( $P=0.0172$ ,  $\chi^2$  for trend), respectively, in patients stratified by tertiles of fibrinogen ( $<3.78$ ,  $3.78$  to  $6.17$ , and  $>6.17$  g/L). The probabilities of a primary end point were 12.1%, 29.7%, and 54.8% ( $P=0.0004$ ), respectively, after stratification of patient data by tertiles of CRP level ( $<5$ ,  $5$  to  $33$ , and  $>33$  mg/L). In multiple logistic regression analysis, higher CRP levels (odds ratio, 2.39; 95% CI, 1.28 to 4.49;  $P=0.0066$ ) and stroke severity on the Canadian Neurological Stroke Scale (odds ratio, 2.37; 95% CI, 1.01 to 5.58;  $P=0.0472$ ) were independently associated with death or new vascular event. **CONCLUSIONS:** Increased levels of CRP are associated with a

worse outcome in patients with ischemic stroke. The increased risk associated with elevated CRP levels is independent of the prognostic influence of fibrinogen.

Stroke 2001 Jan;32(1):133-8

Dilatation of common carotid artery is strongly associated with cerebral ischemic stroke with or without the presence of carotid atherosclerosis.

**Background:** Dilatation of common carotid artery (CCA) was related to age, sex and body height in population studies. It was also considered a compensatory mechanism to carotid atherosclerotic stenosis. The present study examined the risk of CCA dilatation associated with ischemic stroke (IS) and its relations to carotid atherosclerosis, hypertension, hyperglycemia, fibrinogen, cholesterol, HDL-cholesterol (HDL-C), smoking and alcohol consumption. **Methods:** A case-control study was carried on 251 first-ever IS patients (age 40) excluding previous history of myocardial infarction and cancer and 242 non-stroke outpatients. Intraluminal diameter of middle portion of CCA, and plaque thickness in CCA, bulb, internal and external carotid arteries were measured. Information on hypertension and diabetes status and data of life-styles such as smoking and alcohol consumption were collected. Levels of fibrinogen, factor VIIIc, cholesterol, HDL-C and glucose were obtained. **Results:** CCA dilatation was a strong factor for IS (OR=4.13, P=0.0001). It was also associated with hypertension, hyperglycemia, smoking, alcohol consumption, low HDL-C, and high levels of fibrinogen, factor VIIIc, cholesterol and plaque score. The association remained significant with or without each of the following conditions: hypertension (p=0.0001, p=0.0007), hyperglycemia (p=0.0446, p=0.0001), elevated fibrinogen (p=0.0104, p=0.0001) or factor VIIIc (p=0.2458, p=0.0001), hypercholesterolemia (p=0.0238, p=0.0001), decreased HDL-C (p=0.0012, p=0.0001) and presence of plaque score (p=0.0263, p=0.0003). Adjusting above risk factors, odds ratios of elevated diameter could associated with IS, before (OR=2.21, P=0.0066) and after (OR=6.63, p=0.0055) excluding subjects with plaque. **Conclusion:** Dilatation of CCA is a strong risk factor for IS. The fact the association remained significant without ultrasonic evidence of carotid plaque indicates that IS in Chinese involved a mechanism of active vasculopathy, not just a passive compensatory process to extracranial atherosclerosis.

Stroke. 2000;32:365-d

Predictors of progression in lacunar stroke.

**Objective:** To identify predictors of deterioration in patients with lacunar syndromes. **Methods:** We prospectively evaluated 46 consecutive patients (12 women, 34 men; age  $64.5 \pm 13.7$  yrs. [ mean  $\pm$  SD ] ) with acute lacunar stroke by daily clinical neurological examination including NIHSS and follow-up using the Barthel Index after three months. In addition, we determined parameters of inflammation ( C-reactive protein, leukocytes, body temperature), coagulation (d-dimers, fibrinogen, PTT, vWF ), glutamate, as well as blood glucose and blood pressure. Progressive neurological deficit was defined as worsening of the NIHSS by one point in one singular item. **Results:** Eleven patients (23.9 % ) showed a clinical progression of stroke symptoms, 35 patients remained stable or improved. The NIHSS on admission was similar in both groups ( $4.2 \pm 2.7$  vs.  $3.8 \pm 2.2$ ), but significantly higher in progressive patients on day two ( $5.4 \pm 3.5$  vs.  $2.6 \pm 2.0$ ; p=0.02) and at discharge ( $3.7 \pm 3.3$  vs.  $1.6 \pm 1.7$ ; p=0.046). Nine of the 11 progressive patients showed deterioration in the first 24 hours after admission. Barthel Index after 90 days was significantly lower in the progressive patients ( $87 \pm 18$  vs.  $95 \pm 19$ ; p=0.005). Clinical progression was significantly associated with elevated body temperature (p=0.031 ), fibrinogen ( p=0.048 ) and a higher leucocyte count ( p=0.017 ) on admission. Mean blood glucose and blood pressure were also higher in progressive patients, but this difference did not reach the level of significance. There was no significant correlation for the other coagulation parameters, glutamate level on admission, risk factors, age and gender. **Conclusions:** In lacunar stroke there is a high rate (= 23.9 % ) of neurological worsening, and the long-term prognosis of progressive patients is worse compared to non-progressive patients. Progression usually occurs within 24 hours and may be related to an acute-phase response.

Stroke. 2000;32:347-c

Melatonin

Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment.

The objective of the present study was to assess the toxicology of melatonin (10 mg), administered for 28 days to 40 volunteers randomly assigned to groups receiving either melatonin (N = 30) or placebo (N = 10) in a double-blind fashion. The following measurements were performed: polysomnography (PSG), laboratory examinations, including complete blood count, urinalysis, sodium, potassium and calcium levels, total protein levels, albumin, blood glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), urea, creatinine, uric acid, glutamic-oxalacetic transaminase (GOT), glutamic-pyruvate transaminase (GPT), bilirubin, alkaline phosphatase, gama-glutamic transaminase (GGT), T3, T4, TSH, LH/FSH, cortisol and melatonin serum concentrations. In addition, the Epworth Somnolence Scale (ESS) and a sleep diary (SD) were also applied to the volunteers one week before each PSG. In addition, the volunteers were asked about possible side effects (SE) that appeared during the treatment. The study was carried out according to the

following timetable: Visit 0, filling out the term of consent and inclusion criteria; Visit 1, PSG, laboratory examinations, ESS, SD, melatonin serum concentrations; Visit 2, SD, melatonin serum concentrations, SE; Visit 3, melatonin serum concentrations, PSG, ESS, SE; Visit 4, laboratory examinations, SE, melatonin serum concentrations, SD; and Visit 5, PSG, ESS, SE. Analysis of the PSG showed a statistically significant reduction of stage 1 of sleep in the melatonin group. No other differences between the placebo and melatonin groups were obtained. In the present study we did not observe, according to the parameters analyzed, any toxicological effect that might compromise the use of melatonin at a dose of 10 mg for the period of time utilized in this study.

J Pineal Res 2000 Nov;29(4):193-200

Effect of sustained nocturnal transbuccal melatonin administration on sleep and temperature in elderly insomniacs.

Previous research has suggested a role for the pineal hormone melatonin in the control of the body's sleep-wake and thermoregulatory systems. In the elderly population, there have been reports of decreased nighttime secretion of melatonin and suggestions that this may, in turn, be responsible for the increased incidence of sleep disorders reported by this age group. On this basis, it has been suggested that augmented nocturnal melatonin levels may improve sleep quality in age-related sleep disorders. Following screening assessments, 12 elderly (> 55 years) subjects with sleep maintenance insomnia were treated with either 0.5 mg transbuccal melatonin or a placebo for two sessions of four consecutive nights, at least three days apart. Subjects self-selected lights-out times, and sleep was assessed using standard polysomnographic (PSG) measures. Body temperature was measured continually from 2100 to 0700 hour, and sleep quality was assessed from PSG variables measured. Nightly urine samples were assayed for the melatonin metabolite 6-sulfatoxy-melatonin (aMT.6S). Compared to the placebo, transbuccal melatonin administration significantly increased mean nocturnal aMT.6S excretion (mean +/- SEM: 194.2 +/- 16.5 vs. 42.5 +/- 7.7 nmol). In addition, there was a significant reduction in core body temperature relative to the placebo condition ( $p < .05$ ). However, sustained transbuccal melatonin treatment had no positive significant effect on any PSG measure of sleep quality. The results from the present study suggest that sustained nocturnal administration of melatonin, in the low pharmacological range, might be of limited clinical benefit in this subject population.

J Biol Rhythms 1998 Dec;13(6):532-8

Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag.

To compare the impact of various dosage forms of melatonin and placebo on jet lag symptoms, 320 volunteers who had flights over 6 to 8 time zones were recruited for a double-blind, randomized, placebo-controlled study. The volunteers received either melatonin 0.5-mg fast-release (FR) formulation, melatonin 5-mg FR formulation, melatonin 2-mg controlled-release (CR) formulation, or placebo. The study medication was taken once daily at bedtime during four days after an eastward flight. The volunteers completed the Profile of Mood States (POMS), sleep log, and symptoms questionnaires once daily and the Karolinska Sleepiness Scale (KSS) three times daily prior to departure and during the 4 days of medication intake postflight. A total of 234 (73.1%) participants were compliant and completed the study. The FR melatonin formulations were more effective than the slow-release formulation. The 5-mg FR formulation significantly improved the self-rated sleep quality ( $p < .05$ ), shortened sleep latency ( $p < .05$ ), and reduced fatigue and daytime sleepiness ( $p < .05$ ) after intercontinental flight. The lower physiological dose of 0.5 mg was almost as effective as the pharmacological dose of 5.0 mg. Only the hypnotic properties of melatonin, sleep quality and sleep latency, were significantly greater with the 5.0-mg dose.

Chronobiol Int 1998 Nov;15(6):655-66

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Entrainment of free-running circadian rhythms by melatonin in blind people.

**BACKGROUND:** Most totally blind people have circadian rhythms that are "free-running" (i.e., that are not synchronized to environmental time cues and that oscillate on a cycle slightly longer than 24 hours). This condition causes recurrent insomnia and daytime sleepiness when the rhythms drift out of phase with the normal 24-hour cycle. We investigated whether a daily dose of melatonin could entrain their circadian rhythms to a normal 24-hour cycle. **METHODS:** We performed a crossover study involving seven totally blind subjects who had free-running circadian rhythms. The subjects were given 10 mg of melatonin or placebo daily, one hour before their preferred bedtime, for three to nine weeks. They were then given the other treatment. The timing of the production of endogenous melatonin was measured as a marker of the circadian time (phase), and sleep was monitored by polysomnography. **RESULTS:** At base line, the subjects had free-running circadian rhythms with distinct and predictable cycles averaging 24.5 hours (range, 24.2 to 24.9). These rhythms were unaffected by the administration of placebo. In six of the seven subjects the rhythm was entrained to a 24.0-hour cycle during melatonin treatment ( $P < 0.001$ ). After entrainment, the subjects spent less time awake after the initial onset of sleep ( $P = 0.05$ ) and the efficiency of sleep was higher ( $P = 0.06$ ). Three subjects subsequently participated in a trial in which a 10-mg dose of melatonin was given daily until entrainment was achieved. The dose was then reduced to 0.5 mg per day over a period of three months; the entrainment persisted, even at the lowest dose. **CONCLUSIONS:** Administration of melatonin can entrain circadian rhythms in most blind people who have free-running rhythms.

N Engl J Med 2000 Oct 12;343(15):1070-7

Use of slow-release melatonin in treatment-resistant depression.

**OBJECTIVE:** To examine antidepressant augmentation with and hypnotic effects of slow-release melatonin (SR-melatonin) in patients with treatment-resistant depression. **DESIGN:** Open-label trial. **SETTING:** Tertiary care outpatient depression clinic. **PATIENTS:** Nine outpatients who had failed to respond to two or more eight week trials of antidepressant medication. **INTERVENTIONS:** Patients received SR-melatonin 5 mg per day for the first two weeks and 10 mg per day for the final two weeks, in addition to their antidepressant medication. **OUTCOME MEASURES:** Structured Clinical Interview for DSM-IV, Axis 1 Disorders, Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory, Response Style Questionnaire, sleep and fatigue measures. **RESULTS:** One patient was excluded after one week because of the development of a mixed affective state. In the remaining 8 patients there was a 20% mean decrease in HRSD scores after four weeks of treatment, with no individual achieving an improvement of 50% or more. There was a 36% decrease on the three item HRSD related to insomnia, with four of eight patients showing at least a 50% improvement on this measure. The greatest decrease in insomnia occurred during the last two weeks of the study, following the increase in dosage to 10 mg per day of SR-melatonin. Patients also reported significantly lower levels of fatigue post-treatment. **CONCLUSIONS:** SR-melatonin may be a useful adjunct for sleep, but does not substantially augment existing antidepressant therapies in some patients with treatment-resistant depression.

J Psychiatry Neurosci 2000 Jan;25(1):48-52

The hypnotic effects of melatonin treatment on diurnal sleep in humans.

This study investigated the hypnotic effects of 10 mg melatonin and placebo, which were administered at 10.00 hour, according to a single-blind crossover design, on an 8 hour diurnal sleep from 11.00 to 19.00 hour, following a full night of sleep. The subjects were six healthy male students, each of whom underwent polysomnography and rectal temperature monitoring. Melatonin treatment significantly increased total sleep time in diurnal sleep (403.2 $\pm$ SD 72.8 min and 258.5 $\pm$ 118.3 min,  $P < 0.001$ ). As to changes in rectal temperature during diurnal sleep, however, there were no significant differences between the melatonin and placebo conditions. Thus, these results indicated that melatonin administered at 10.00 hour had direct hypnotic effects on diurnal sleep.

Psychiatry Clin Neurosci 1999 Apr;53(2):243-5

Effects of a low dose of melatonin on sleep in children with Angelman syndrome.

The effects of low dose melatonin therapy on sleep behavior and serum melatonin levels were studied in Angelman syndrome (AS) children suffering from insomnia. 24-hour motor activity was monitored in 13 AS children (age 2-10 yr) in their home environments for seven days prior to melatonin treatment and for five days during which a 0.3 mg dose of melatonin was administered daily 0.5-1

hour before the patient's habitual bedtime. Blood samples were with-drawn at hourly intervals over two 21 hour periods in order to measure individual endogenous serum melatonin levels and the levels induced by melatonin treatment. Actigraphic recording of motor activity, confirmed by parents' reports, showed a significant improvement in the patients' nocturnal sleep pattern as a result of melatonin treatment. Analysis of the group data revealed a significant decrease in motor activity during the total sleep period following melatonin treatment, and an increase in the duration of the total sleep period. Endogenous peak nocturnal melatonin values ranged from 19 to 177 pg/ml. The administration of melatonin elevated peak serum hormone levels to 128 to 2800 pg/ml in children of different ages and body mass. These data suggest that a moderate increase in circulating melatonin levels significantly reduces motor activity during the sleep period in Angelman syndrome children, and promotes sleep.

J Pediatr Endocrinol Metab 1999 Jan-Feb;12(1):57-67

Melatonin treatment of non-epileptic myoclonus in children.

Oral melatonin (MLT) has been used by our Vancouver research group in the treatment of paediatric sleep disorders since 1991; slightly over 200 children, mainly with multiple disabilities, who frequently had seizures, have been treated. Three children with markedly delayed sleep onset due to recurring myoclonus were also referred for MLT treatment: two had non-epileptic, and one had epileptic and non-epileptic myoclonus. Low doses of oral MLT (3 to 5 mg) unexpectedly abolished their myoclonus and allowed them to sleep. There were no adverse effects. It appears that certain types of myoclonus, which might be resistant to conventional anticonvulsant medications, may respond to MLT but the mechanism of action is unclear. Further research on this novel treatment is urgently needed.

Dev Med Child Neurol 1999 Apr;41(4):255-9

Serum melatonin kinetics and long-term melatonin treatment for sleep disorders in Rett syndrome.

We studied the circadian rhythm of serum melatonin levels in two patients with classical Rett syndrome having severe sleep disorders; serum melatonin levels were measured before and during melatonin treatment using radioimmunoassay. Patient 1 had a free-running rhythm of sleep-wake cycle from three years of age. At the age of four years, the peak time of melatonin was delayed six hour compared to normal control and the peak value was at the lower limit. Patient 2 had a fragmented sleep pattern accompanied by night screaming from 1 year and 6 months of age. At the age of 10 years, the peak time of melatonin secretion was normal but the peak value was at the lower limit. These patients were given 5 mg melatonin orally prior to bedtime. Exogenous melatonin dramatically improved the sleep-wake cycle in patient 1. In patient 2, exogenous melatonin showed a hypnotic effect but early morning awakenings occurred occasionally. When melatonin treatment was stopped, the sleep disorders recurred and re-administration of 3 mg melatonin was effective in both patients. The effect was maintained over two years without any adverse effects. These findings suggests that sleep disorders in patients with Rett syndrome may relate with an impaired secretion of melatonin.

Brain Dev 1999 Jan;21(1):59-62

Melatonin in sleep rhythm disorders after cerebral stroke.

Small doses of melatonin were administrated to 30 patients with day/night rhythm disorders, after cerebral stroke. Psychotropic drugs administrated before did not bring any clinical improvement. In evaluation of melatonin the time till falling asleep, sleep duration, anxiety and the following day activity were taken into account. Good results were observed in majority of patients, concerning falling asleep and sleep were obtained continuity. The melatonin is a safe and worth drug in sleep rhythm disorders in patients after cerebral stroke.

Pol Merkuriusz Lek 2000 Jun;8(48):411-2

Effect of melatonin in selected populations of sleep-disturbed patients.

In an open pilot study on the efficacy of melatonin in the treatment of sleep disorders, patients with sleep disturbances alone, patients with sleep disturbances and signs of depression and patients with sleep disorders and dementia received 3 mg melatonin p.o. for 21 days, at bed time. After 2 to 3 days of treatment, melatonin significantly augmented sleep quality and decreased the number of awakening episodes in patients with sleep disturbances associated or not with depression. Estimates of next-day alertness improved significantly only in patients with primary insomnia. Agitated behavior at night (sundowning) decreased significantly in dementia patients. In a second retrospective study, 14 Alzheimer's disease (AD) patients received 9 mg melatonin daily for 22 to 35 months. A significant improvement of sleep quality was found, while there were no significant differences between initial and final neuropsychological evaluation (Functional Assessment Tool for AD, Mini-Mental). The results indicate that melatonin can be useful to treat sleep disturbances in elderly insomniacs and AD patients.

Melatonin treatment in an institutionalised child with psychomotor retardation and an irregular sleep-wake pattern.

An institutionalized 13 year old girl with psychomotor retardation suffered from an irregular sleep-wake pattern. Multiple measurements of urinary sulphatoxy-melatonin (aMT6) concentrations were abnormally low, without any significant day-night differences. Administration of exogenous melatonin (3 mg) at 18:00 resulted in increased nocturnal urinary aMT6 concentrations and improvements in her sleep-wake pattern. Melatonin may help disabled children suffering from sleep disorders.

Arch Dis Child 1998 Jul;79(1):63-4

Melatonin treatment for rhythm disorder.

We tried melatonin treatment in two patients with non-24 hour sleep-wake syndrome, who did not respond to treatments by vitamin B12, bright light therapy, or hypnotics. In one patient, melatonin 5 to 10 mg improved difficulty in falling asleep and in waking, although it failed to improve the sleep-wake rhythm. In another patient, melatonin 3 mg successfully changed the sleep-wake rhythm from free-running pattern to delayed sleep phase pattern. However, melatonin re-administration after a four month drug-free interval failed to improve his free-running sleep-wake rhythm. These results suggest that melatonin acted as a sleep inducer in one patient and as a phase setter in the other, although the effect on the latter patient was transient.

Psychiatry Clin Neurosci 1998 Apr;52(2):262-3

Melatonin treatment for circadian rhythm sleep disorders.

We administered 1 to 3 mg melatonin to 11 patients (eight men, three women, aged 16 to 46 years) with circadian rhythm sleep disorders; nine with delayed sleep phase syndrome and two with non-24-hour sleep-wake syndrome. Sleep logs were recorded throughout the study periods and actigraph and rectal temperature were monitored during treatment periods. Melatonin was administered 1 to 2 hour before the desirable bedtime for expected phase-shifting, or 0.5 to 1 hours before habitual bedtime for gradual advance expecting an hypnotic effect of the melatonin. Melatonin treatments were successful in 6/11 patients. Timing and dose of melatonin administration, together with its pharmacological properties for circadian rhythm sleep disorders, should be further studied.

Psychiatry Clin Neurosci 1998 Apr;52(2):259-60

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