Demência e Diminuição da Cognição e Procaína

01/03/2009

Procaine treatments for cognition and dementia

Szatmári Szabolcs, Bereczki Dániel

This review should be cited as: Szatmári Szabolcs, Bereczki Dániel. Procaine treatments for cognition and dementia (Cochrane Review). In: The Cochrane Library, Issue 4, 2008. Oxford: Update Software.

Abstract

Background
Procaine is a controversial substance which has been used for "antiageing" effects including cognitive improvement for more than 50 years.
Objective
To assess the efficacy and adverse effects of procaine (and preparations containing procaine as a component) on cognitive function in the treatment of people with dementia as well as healthy elderly people.
Search strategy
References regarding trials with people with dementia or cognitive impairment were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 8 September 2007 using the search terms: gerovital* or aslavital* or procain* or KH3 or novocain* or GH3 or trofibial or "Zell H3" or Vitacel* or GH7 or "Ultimate 9". The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 18 September 2007 to find references to trials with healthy people.
Selection criteria
All human, unconfounded, randomized double-blind trials in which treatment with procaine was administered for its effects on cognitive function and behavioural symptoms in demented or healthy elderly participants in parallel group comparison with placebo.
Data collection and analysis
The two review authors independently selected trials, assessed quality, extracted data, and performed the data analysis.
Main results
Pooling data from two studies showed a detrimental effect of procaine in terms of causing side effects (20/208 active versus 3/207 placebo, OR 7.30, 95% CI 2.13 to 25.02, P = 0.002). In patients with dementia, a single small study also suggested a detrimental effect. Two trials referring to healthy elderly persons suggested a positive effect of procaine preparation on cognitive function. Meta-analysis of beneficial outcomes was not appropriate due to the different preparations, durations and poor quality of trials. Most trials were performed before the 1990s and none reported any criteria for cognitive decline and dementia.
Reviewers' conclusions
This review suggests that the evidence for detrimental effects of procaine and its preparations is stronger than the evidence for benefit in preventing and/or treating dementia or cognitive impairment.

Synopsis

Preparations which contain procaine as a component are widely promoted and used in several countries.
In analysing the effect of procaine and its preparations, there was no evidence for benefit in the prevention or treatment of dementia or cognitive impairment.
There were a few but some serious adverse events related to long-term use of procaine.

Background

Dementia is an important public health problem. As the prevalence of dementia increases with age, and the proportion of the elderly in the world population is expected to increase over time, the impact of dementia on society will increase. More effective primary prevention might result in a decrease in the prevalence of dementia. Pharmacological and non-pharmacological treatments have been developed which aim to treat the causes of dementia as well as to interrupt the disease. Many other drugs have been claimed to provide symptomatic or disease-modifying effects.
Procaine hydrochloride or novocaine was first synthesized by the German chemist Alfred Einhorn in 1905 and was used as a local anaesthetic. Administered intravenously from 1925, it was described as effective in migraine, pain, and asthma. After 1950 it was also used for its "antiageing" effects. Preparations which contain procaine as a component (e.g. Gerovital, Gerovital H3, Procaine Hydrochloride, KH3, GH3, Trofibial H3, Aslavital, or Zell H3) are claimed to prevent, reverse and interrupt dementia and to have the following beneficial effects: neuron regeneration, cell membrane modulation, protection against cerebral anoxia (a condition in which there is a lack of oxygen supply of the brain), antioxidant activity, increasing resistance to infections and toxins, antidepressant activity (as a reversible inhibitor of monoaminoxidase), increasing serum HDL-C concentrations and decreasing triglyceride levels. They are also claimed to be thyroid inhibitors, muscle relaxants and antihistamines. They are said to decrease plasmacortisol levels and therefore to have an anti-stress effect, helping to prevent dementia. In the United States, the Food and Drug Administration banned Gerovital H3 from interstate commerce as an unapproved drug and, since 1982, has prohibited its importation although there are indications that it, or its compounds, may still be imported under the category of a "nutrient". Whether characterized as drug or nutrient, the FDA's 1982 automatic detention alert is still in effect and bans the import of Gerovital H3 into the US as "a new drug without an approved new drug application" (FDA 1982).
In 1977 an independent review of procaine based interventions for the elderly was carried out by Ostfeld (Ostfeld 1977). He reviewed all available evidence from randomized and controlled trials and concluded that there was no convincing evidence that procaine or combined drugs containing procaine had a prophylactic or therapeutic effect in pathological ageing or in the diseases of later life, including dementia. Despite this, the drugs continue to be widely promoted and can be purchased "over the counter" outside the US and via the Internet. The following websites demonstrate the intensity of these marketing efforts:
http://www.realgerovital.com, http://www.cellhealthmakeover.com, http://www.achilleshealthmart.com, http://whiteharvest.com/, http://www.herbalremedies.com/procaine1.html, http://www.ultimate9.com, http://www.hwize.com/gerovital-gh3/gerovital-gh3.html, http://www.smart-drugs.com/ias-gh3-antiaging.htm, http://www.gh3.co.uk/
The preparations themselves vary widely in active ingredients, nutritional components and other ingredients. The following are examples

of the preparations available as of April 2008:
(1) Gerovital H3, GH3Â® - potassium metabisulphite, benzoic acid and disodium phosphate as well as procaine. VITACEL 3 and VITACEL 3sp are very similar products. Vitacel 6 is GH3 without bisulfite.
(2) ZELL H3, VITACEL 5 - procaine plus various vitamins, minerals and enzymes
(3) KH3 - procaine, hemato porphyrine, and other ingredients
(4) Aslavital is Gerovital H3 + vitamin B6 and other ingredients
(5) VITACEL 4 ASLAVITAL is Aslavital + Bee Propolis + Royal Jelly
(6) Vitacel GH7 or GH7 - procaine hydrochloride complexed with various vitamins and other biologically active compounds.
A host of GH7 based treatments have entered the market:
VITACEL 9* - GH7 + L-Carnitine + CoQ10 + Lycopene
VITACEL 8* - GH7 + Grape Seed + Ginkgo + Milk Thistle + Artichoke extracts
VITACEL GH7* PLUS 200 mg - double dose of GH7
VITACEL 7 GOLD* - a liquid preparation of GH7
Ultimate 9 (also called Procaine Vitamin H3, Ultra GH9, Ultra-H3): in Ultimate 9, so it is claimed, all the procaine hydrochloride is complexed and protected which makes it theoretically six times more active than GH3 (Ultimate 9 2008).
All these products can be sold (like any other product) at whatever price the distributor wishes. Consumers are warned however that "it is worth bearing in mind that a 'cheap' version often indicates corners have been cut in the manufacturing process" (GH3 2008).
At present procaine hydrochloride and preparations containing procaine as a component have an unclassified status as treatments for promoting cognition and preventing dementia. In view of the fact that the last systematic review of preparations containing procaine was performed more than 30 years ago, and given their apparent popularity as an "antiageing" treatment - the preparations are said to be readily available in over 70 countries around the world and to be used by more than 100 million people (GH3 2008) - a Cochrane review testing the safety and efficacy of these preparations for promoting cognition and preventing dementia was warranted.

References to studies included in this review

Balaceanu 1989 *{published data only}*
Balaceanu Stolnici C, Manoiu A, Vrabiescu M. Gerovital h3 effects upon human cognitive behaviour and psychomotor capacity. Romanian Journal of Gerontology and Geriatrics 1989;10:277-84.
Cashman 1961 *{published data only}*
Cashman MD, Lawes TGG. A controlled trial of "Gerioptil". BMJ 1961;1:554-6.
Hall 1983 *{published and unpublished data}*
Hall MR, Briggs RS, MacLennan WJ, Marcer D, Robinson MJ, Everett FM. The effects of procaine/haematoporphyrin on age-related decline: a double-blind trial. Age and Ageing 1983;12:302-8.
Southampton 1982 *{unpublished data only}*
The Southampton Ageing Project: A trial of KH3. 1982:-.
** indicates the major publication for the study*

References to studies excluded from this review

Abrams 1965 *{published data only}*
Abrams A, Tobin S, Gordon P, Pechtel C, Hilkevitch A. The effects of a European procaine preparation in an aged population. Journal of Gerontology 1965;20:139-43.
Aslan 1980 *{published data only}*
Aslan A. A new method for prophylaxis and treatment of aging with novocain-eutrophic and rejuvenating effects. Therapiewoche 1956;7:14-22.
Aslan A, Vrabiescu A, Dobre M. Aslavital for children in mentally deficient subjects. Romanian Journal of Gerontology and Geriatrics 1980;1:189-94.
Aslan A, Vrabiescu A, Dobre M, Polovrageanu E. The aslavital treatment in the recovery of mentally-deficient children. Romanian Journal of Gerontology and Geriatrics 1980;1:93-8.
Berryman 1961 *{published data only}*
Berryman JAW, Forbes HAW, Simpson-White R. Trial of procaine in old age and chronic degenerative disorders. BMJ 1961;2:1683-4.
Czerwenka 1970 *{published data only}*
Czerwenka H, Maly J, Quatember R, Tschabitscher H. Clinical and psychological investigations with a geriatric substance (in German). Wiener Medizinische Wochenschrift 1970;120:217-24.
Fee 1961 *{published data only}*
Fee SR, Clark ANG. Trial of procaine in the aged. BMJ 1961;2:1680-2.
Gericke 1961 *{published data only}*
Gericke OL, Lobbv LG, Pardoll DH. An evaluation of procaine in geriatric patients in a mental hospital. Journal of Clinical and Experimental Psychopathology 1961;22:18-33.
Hirsch 1961 *{published data only}*
Hirsch J. A clinical trial of procaine hydrochloride. BMJ 1961;2:1684-5.
Isaacs 1962 *{published data only}*
Isaacs B. Trials of procaine in aged patients. BMJ 1962;2:188-9.
Kant 1962 *{published data only}*
Kant S, Sterne DM. Evaluation of chronically ill patients treated for one year with procaine. Journal of the American Geriatrics Society 1962;10:408-12.
Kent 1982 *{published data only}*
Kent S. The procaine "youth" drugs. Geriatrics 1982;37:32-6.
Long 1964 *{published data only}*
Long RF, Gislason SS. The effect of procaine on orientation, attention, memory and weight of aged psychiatric patients. Journal of Neuropsychiatry 1964;5:186-96.
May 1962 *{published data only}*
May RH, Ruland MB, Bylenga ND, Peppel HH. Prolonged procaine therapy in geriatric psychiatric patients. Geriatrics 1962;17:161-8.
Olsen 1978 *{published data only}*
Olsen EJ, Bank L, Jarvik LF. Gerovital-H3: a clinical trial as an antidepressant. Journal of Gerontology 1978;33:514-20.
Ostfeld 1977 *{published data only}*
Ostfeld A, Smith CM, Stotsky BA. The systemic use of procaine in the treatment of the elderly: a review. Journal of the American Geriatrics Society 1977;5:1-19.
Quatember 1980 *{published data only}*
Quatember R, Maly J. Neuropsychological methods of examination of age-specific performance parameters. Wiener Medizinische Wochenschrift 1980;130:688-92.
Rusu 1996 *{published data only}*
Rusu C, Borsa C, Gradinaru D, Ionescu C, Babeanu S. Antioxidant and lipid-lowering effects of the original procaine-based products. Romanian Journal of Gerontology and Geriatrics 1996;18:47-61.
Sakalis 1974 *{published data only}*
Sakalis G, Oh D, Gershon S, Shopsin B. A trial of gerovital H-3 in depression during senility. Current Therapeutic Research, Clinical and Experimental 1974;16:59-63.
Smigel 1960 *{published data only}*

Smigel JO, Piller J, Murphy C, Lowe C, Gibson J. H-3 (procaine hydrochloride) therapy in aging institutionalized patients: an interim report. Journal of the American Geriatrics Society 1960;8:785-94.

Valtonen 1992 *{published data only}*
Valtonen EJ. Procaine chloride as a universal remedy for somatic and psychic symptoms. Suomen Lookorilehti 1992;47:1608-11.

Zdichynec 1977 *{published data only}*
Zdichynec B. Successes in novocain therapy in the control of premature ageing. Z Alternsforsch 1977;32:267-9.

Zwerling 1975 *{published data only}*
Zwerling I, Plutchik R, Hotz M, Kling R, Rubin L, Grossman J. Effects of a procaine preparation (Gerovital H3) in hospitalized geriatric patients: a double-blind study. Journal of the American Geriatrics Society 1975;23:355-9.

Additional references

APA 1987
In: Diagnostic and Statistical Manual of Mental Disorders Washington, DC: American Psychiatric Association, 1987:-.

DSM IV 1994
Diagnostic and Statistical Manual of Mental Disorders. In: American Psychiatric Association. Vol IV Washington, DC, USA: American Psychiatric Publishing, 1994:-.

FDA 1982
Automatic detention alert for Gerovital. :-.

GH3 2008
:-.

Higgins 2008
Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 [updated February 2008]. :-.

McKhann 1984
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;4:939-44.

Román 1993
Román CG, Tatemichi TK, Erkinjuntti T. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250-60.

Ultimate 9 2008
Development of Ultimate 9. :-.

WHO 1992
In: International classification of diseases, 10th revision Geneva: World Health Organisation, 1992:-.