

Published in final edited form as:

Alzheimers Dement. 2015 January ; 11(1): 99–103. doi:10.1016/j.jalz.2014.01.006.

A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's

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Keywords

ketone bodies; β -hydroxybutyrate; pyruvate dehydrogenase; brain insulin resistance; fasting; ketogenic diet; medium-chain triglyceride; ketone monoester

1. Background

Impairment of the brain's glucose utilization is an early feature of Alzheimer's disease (AD) and may contribute to its causation and progression[1,2]. In patients with preclinical AD, fluorodeoxyglucose-positron emission tomography (FDG-PET) discloses a consistent pattern of reduction in the cerebral metabolic rate of glucose (CMRglu) in the posterior cingulate, parietal, temporal, and prefrontal locations[3]. Clinical AD symptoms almost never occur without such CMRglu decreases[3], which may be associated with local brain insulin resistance[4].

To the extent impairment of glucose utilization contributes to AD's pathogenesis, providing the AD brain with sufficient ketone bodies(KB)—the brain's principal alternative fuel during prolonged fasting[5,6]—would likely mitigate the energy deficit, as shown in Fig. 1.

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*KME was always taken mixed with soda-flavored syrups (25% syrup, 25% KME, 50% water) to help mask its disagreeable taste. The KME mixture was invariably well tolerated.

Conflict-of-interest statements:

Dr. Newport, Dr. VanItallie, and MT King have no financial interest in ketone monoester. Dr. VanItallie is a minority shareholder in a company that produces a food product containing medium-chain fatty acids. Dr. Veech has patent right from invention determined by NIH and DHHS standards.

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However, to deliver enough KB-derived energy to glucose-deprived parts of the AD brain, it is necessary to raise plasma KB levels significantly above the 0.2 mM default concentrations customary in metabolically normal individuals (6,7). As shown in Figure 1, KB-derived acetyl-CoA enters the pathway to the Krebs (tricarboxylic acid [TCA]) cycle distal to the rate-limiting mitochondrial enzyme, pyruvate dehydrogenase (PDH), thus bypassing blocks in glucose utilization such as that caused by the inhibiting effect of insulin resistance on PDH activity [8,9].

Plasma ketone levels most expedient for rescue of still viable, energy-starved parts of the AD brain are unknown; however, during hyperketonemia, the rate-limiting step for KB utilization is their transport into brain, with utilization rate increasing nearly proportionally with plasma KB concentration[10]. In 8 healthy young adults, daily administration of 20g of medium-chain triglyceride(MCTG) for one week, followed by 30g/d for 3 weeks, raised plasma KB levels to a mean value throughout the study day of 0.29mM, with a peak level of 0.48mM. This degree of hyperketonemia was estimated to contribute up to 9% of brain energy metabolism[7].

2. Established methods for inducing therapeutic hyperketonemia

Established methods for inducing therapeutic hyperketonemia have entailed adherence to a ketogenic diet(KD)[11] and/or repetitive ingestion of MCTG[12]. Successful adherence to the very-high-fat, very-low carbohydrate classical KD requires strong motivation in patients and caregivers. Liberalized versions may provide clinical benefit at lower plasma ketone levels[11].

Prolonged KD consumption may increase levels of atherogenic lipids and produce other adverse effects[6,11]. After 8 weeks on a very-low-carbohydrate diet (5–10% of calories), a group of elderly individuals with mild cognitive impairment (MCI) exhibited improved verbal memory performance ($p = 0.01$)[13].

MCTG users can elevate plasma ketone levels while continuing their usual diet. In a cohort of patients with MCI and AD given 20g of MCTG/d, β HB concentrations rose from ~0.09 mM(pre-dose) to 0.3–0.4 mM(2h post-dose). During hyperketonemia, cognitive performance significantly improved—but only among subjects who were apolipoprotein E (*APOE*) $\epsilon 4$ allele-negative [12]. The highest KB levels appeared to confer most benefit. About 12.5% of the subjects discontinued participation because of minor gastrointestinal side effects.

3. A novel, direct approach to the production of therapeutic hyperketonemia

Herein, we report the first use, in a patient with younger-onset sporadic AD, of a potent ketogenic agent, (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (referred to herein as ketone monoester[KME])[14]. KME has undergone extensive animal[15] and human toxicity tests[14], and meets FDA GRAS standards. KME improves cognitive performance and reduces $A\beta$ and tau deposition in cognition-relevant areas in a mouse AD model[16].

After ingestion, KME is fully hydrolyzed in the small intestine, yielding (i) β HB, carried to the systemic circulation, and (ii) 1,3-butanediol, metabolized in liver to acetoacetate (AcAc) and β HB[15].

Study of KME's kinetics, safety and tolerability in 27 men and 27 women found that, compared to the inconvenience of preparing and consuming a KD, KME ingestion is a safe and simple method for temporarily elevating plasma KB to c. 4.5 mM within 1–2h after ingestion of 714mg/kg [14].

4. Clinical response of a patient with AD dementia to KME treatment

4.1 The patient (TP)

TP is a 63-year-old Caucasian male, former accountant, with younger-onset, sporadic Alzheimer's disease (AD) for 12 years. In 2001, at age 51, he began to complain of short-term memory loss, initially attributed to depression. The condition inexorably worsened and, during 2006, he had to give up his job and stop driving. By then, he was displaying characteristic features of AD dementia, including increasingly severe memory loss, poor concentration and organization, misplacing important items, inability to carry out activities of daily living, and inability to spell and read. Between 2004 and 2008 his Mini-Mental State Examination (MMSE) score declined from 23 to 12. Brain MRI on 8/18/2004 was reported normal; however, MRI on 6/16/2008 showed diffuse involuntional changes of frontal and parietal lobes and moderate left-sided and severe right-sided atrophy of amygdala and hippocampus, consistent with AD. He was found to be *APOE* ϵ 4-positive.

4.2 Initial treatment with ketogenic medium-chain (C8 [caprylic] and C10 [capric]) fatty acids (MCFA)

Because of published information[17] suggesting MCTG-induced increases in plasma ketone levels might benefit AD patients, TP was initially placed, on May 21, 2008, on 35 ml coconut oil (CO) once daily [CO contains ~15% ketogenic MCFA]. Then, over several months, MCTG was added and increased gradually to a 4:3 mixture with CO, eventually reaching 165 ml/d divided into 3–4 servings. Use of the MCTG/CO mixtures as dietary supplements was associated with rapid improvement in TP's personality, mood, and tremor. MMSE improved from 12, measured on May 9, to a high of 20, 75 days later. During the ensuing year, additional gradual improvement occurred in gait, social participation, word finding and recall of recent events. Thus, during MCFA treatment for twenty months, TP showed considerable cognitive improvement (ADAS-Cog [Alzheimer's Disease Assessment Scale-Cognitive] rose 6 points and ADLs [Activities of Daily Living] rose 14 points), followed by stabilization. MRI findings on 4/28/2010 were no different from those on 6/16/2008. Hence, during the two-year period of MCTG/CO treatment, TP's brain remained MRI-stable.

During the winter of 2010, while participating in a crossover clinical trial of the γ -secretase inhibitor, semagacestat, TP retrogressed when shifted from placebo to drug. The deterioration, which presumably resulted from semagacestat-induced collateral damage to other proteins affecting neurocognitive function [18], persisted after the drug was stopped. It is now known that TP was on placebo during at least the initial twelve months of the study.

He discontinued participation in the study March 1, 2010, owing to new problems appearing in the prior month, including poor wound healing, fainting, elevated CPK (non-cardiac), a respiratory infection, and outbreak of fever blisters. Also, throughout February and March 2010, he became increasingly depressed and began to experience confusion with images in the mirror and his whereabouts in the home. He began wandering, lost interest in yard and house work, and required step-by-step instruction and considerable assistance to dress and complete hygiene-related tasks.

4.3 Clinical response to treatment with ketone monoester (KME)

As TP's condition worsened, his wife/caregiver, a neonatology specialist, became increasingly desperate for a remedy. Searching for new treatments, she found several articles[6,19,20] suggesting that, in certain AD patients, ketone-ester induced elevation of plasma KB to levels approximating to those obtained during a fast, might prove more effective than the lower concentrations achievable by MCTG administration[7,12].

On April 29, 2010, with his full cooperation and consent, TP was started at home on orally administered KME. Throughout KME treatment, TP remained on his usual diet and also continued to take the MCTG/CO mixture, as described in 4.2.

During the first two KME days, TP received 21.5g thrice daily. Thirty minutes of video taken between 2 to 3 hours following the first dose of KME demonstrate a marked improvement in mood and the ability to recite and write out the complete alphabet, which he had been unable to do for many months. The next morning he spontaneously chose clothes and dressed himself—also a new development. On third day of KME treatment, the amount administered was increased to three 28.7g servings/d. Following serving- size increase, he began to initiate and complete many other activities without prompting or assistance.

These included showering, shaving, brushing teeth, finding his way around the house, choosing and ordering food from a menu, and distributing utensils from the dishwasher. These activities had not been observed for months before KME was started. Abstract thinking, insight, and a subtle sense of humor returned to his conversation. In his own assessment of his response to KME, he stated that he felt “good”, had “more energy” and was “happier.” He also found it “easier to do things” – which coincided with the caregiver's observations.

After six to eight weeks of taking 28.7g of the KME thrice daily, he began to exhibit improvement in memory retrieval, spontaneously discussing events that occurred up to a week earlier. He was again able to perform more complex tasks, such as vacuuming, washing dishes by hand, and yard work.

Plasma β HB levels were measured occasionally to assess KME-plasma β HB dose-response relationships (Fig. 2). Noticeable improvements in performance (conversation, interaction) were observed at higher, post-dose β HB levels, compared to pre-dose values.

Of a battery of commonly ordered blood chemistry tests done on TP before and during KME treatment, the only noteworthy changes were in certain plasma lipids. Over 20 months, total

cholesterol fell from a pre-KME mean (n=2) of 244 to 163mg/dl. HDL cholesterol fell from 85 to 68mg/dl, and LDL cholesterol from 145 to 81mg/dl.

4.4 Discussion

The fact that relatively high plasma KB levels (6–8mM) can be maintained indefinitely when KME is ingested at 3–4h intervals may raise questions about the long-term safety of this degree of hyperketonemia. Before KME became available, the only way to obtain comparable plasma KB elevations was by prolonged fasting [5] or strict adherence to a very-high-fat, very-low-carbohydrate KD [11]. Because these methods have confounding metabolic side effects, such as dehydration, urate nephrolithiasis, substantial weight changes, and amenorrhea [21], neither can serve as a satisfactory test for the long-term safety of KME-induced hyperketonemia. Nevertheless, three severely obese inpatients who sustained mean KB levels of ~8mM while undergoing 5–6 weeks of starvation for weight loss did not exhibit adverse clinical effects attributable to the protracted hyperketonemia [5].

In rare instances, hyperketonemia, by reducing renal uric acid clearance, can raise plasma uric acid to levels sufficient to precipitate a flare in gout-susceptible individuals [22]. Drugs that inhibit uric acid synthesis can prevent this complication.

At present, there is no evidence that, by itself, chronic hyperketonemia (at concentrations of ~8-mM) may be clinically unsafe. However, if valid safety issues arise, they should be considered in the light of a possible beneficial effect of KME on such devastating diseases as AD, and on disabling convulsions in infants and children who are refractory to antiepileptic medications[23].

Given the report by Henderson et al. [12] indicating that the *APOE* ϵ 4-positive subjects in their study failed to show statistically significant improvement in their ADAS-Cog scores in response to MCTG treatment, it is noteworthy that TP, although *APOE* ϵ 4-positive, exhibited clear cognitive and behavioral improvement while consuming equivalent or larger quantities of ketogenic, medium-chain fatty acids. The findings of Henderson et al. (which may have lacked the statistical power to detect a change in *APOE* ϵ 4-positive subjects) do not rule out the possibility that carriers of the ϵ 4 allele could show cognitive improvement if studied for longer periods of time and/or given higher doses of MCTG.

5. Conclusion

KME-induced hyperketonemia is robust, convenient, and safe, and the ester can be taken regularly as a food supplement without need to change the habitual diet.

In treatment of TP's long-standing AD dementia, KME-produced repeated diurnal elevations of circulating β HB levels were clearly effective, during the 20-month study, in improving behavior, and cognitive and daily-activity performance. The physician-caregiver noted that performance seemed to track plasma ketone concentrations, with conversation and interaction declining as levels fell toward baseline. From requiring almost constant supervision, TP became much more self-sufficient on KME. However, generalizability of

TP's partial improvement during KME treatment (it cannot be called a "cure") remains to be determined by appropriately designed case-control studies.

6. Research in context

Systematic review

The authors used PubMed and published lectures to assess evidence that (i) AD patients exhibit impairment of glucose utilization in brain areas concerned with memory and cognition; (ii) such impairment may contribute to AD's pathogenesis; (iii) induced elevation of plasma ketone bodies can bypass metabolic blocks to the brain's glucose utilization.

Interpretation

Evidence for impairment of glucose utilization was strong but how much was attributable to neuronal atrophy was unclear. Although some AD patients showed modest cognitive improvement when plasma ketone concentrations were elevated by carbohydrate restriction or medium-chain triglycerides, the clinical advantage of raising plasma ketones to substantially higher levels was unknown.

Future directions

New evidence is provided herein that substantial increases in plasma ketone levels made possible by ingestion of a novel ketone monoester may be associated with enhanced clinical benefit in at least some AD patients. This preliminary observation requires confirmation by properly designed case-control studies.

Acknowledgments

The authors thank Anne B. Pierson, MD, MPH, for helpful editorial assistance.

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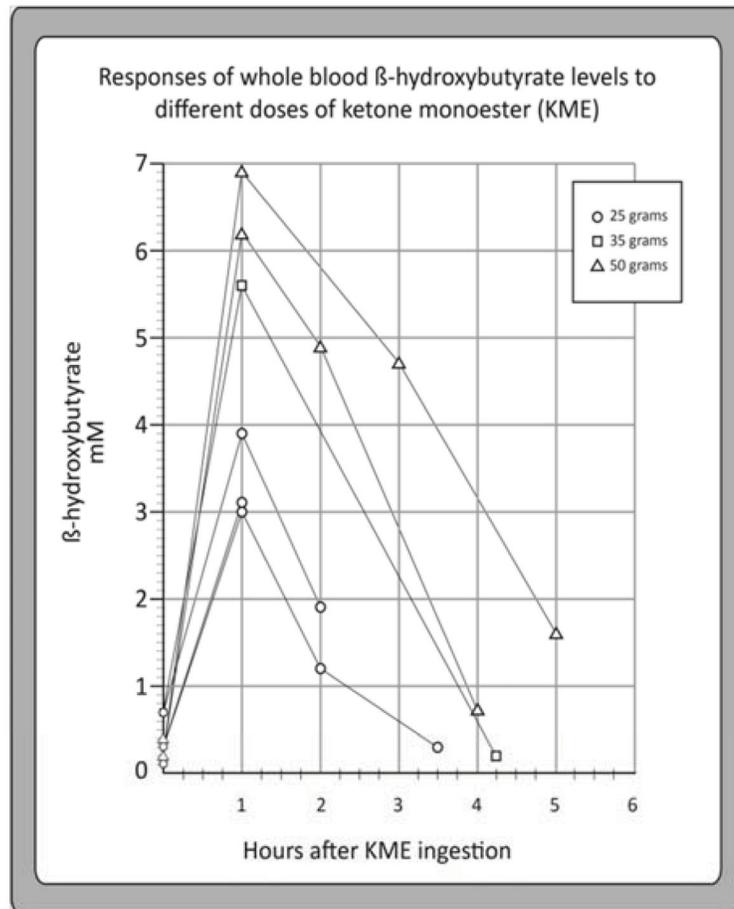


Figure 2.

β -hydroxybutyrate (β HB) concentrations rose to 3–7mM one hour after ingestion of ketone monoester (KME) in three different doses, 25g, 35g, and 50g, taken on separate days. The peak levels measured are in the range of those obtained during adherence to the classical ketogenic diet, and are about tenfold the concentrations achievable by medium-chain triglyceride (MCTG) administration. Because no more than two β HB measurements were made during the first 2 hours after KME ingestion, higher levels might have been reached that were not detected. The findings suggest that substantially elevated blood ketone concentrations can be maintained throughout the day if KME is taken every 3–4 hours. *Precision Xtra Glucose and Ketone Monitoring System*[®] (Abbott) was used to measure β HB levels in capillary blood samples. Acetoacetate (AcAc), ordinarily a minor fraction of total blood ketones, was not measured.