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THE USE OF HERBAL PRODUCTS IN DEMENTIA: EXPERIENCE OF KIPPO IN FOUR NIGERIANS.

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ABSTRACT

Modern neuroimaging and other investigative techniques have provided a lot of new information on the neurobiology of the dementias. Unfortunately no permanent cure has been found for this debilitating disease, giving rise to continuing trial of various products. Alternative and herbal medicine has become popular in neuropsychiatric disorders including dementia.

In this report, we present our experience with Kippo – a Japanese herbal product – in 4 Nigerians with dementia. Two of the patients fully completed the study. The ten word list learning test, community screening interview for dementia (CSI –D), structured dementia interview (SIDAM) and the Geriatric Mental State schedule (GMS) were used to identify dementia according to ICD – 10 diagnostic criteria.

Dementia behaviour disturbance scale (DBD) and modified 22 – item mini – mental state examination (MMSE) were used to evaluate the product efficacy over 8 weeks. One patient showed some initial improvement on the DBD without effect on the MMSE and the other patient showed some initial improvement on the MMSE without effect on the DBD. Both patients had worsening on the clinical Global Impression Scale (CGI) within the study period.

There were no demonstrable adverse effects as shown by physical examinations and laboratory tests. No definite conclusion could be drawn on the efficacy and safety of Kippo in dementia in this short study. We recommend a well controlled larger scale investigation of the effect of Kippo on well defined different subtypes of dementia.

KEY WORDS: Dementia, Herbal products, Kippo.

INTRODUCTION

Recent developments in neuro-imaging techniques and molecular biology have provided considerable wealth of information on the structure and functioning of brains of persons with Alzheimer's disease and other dementias. There has been a literal explosion of research into the dementias by the close of the 20th century[1].

Unfortunately, these developments have not been matched by therapeutic methods effective in ameliorating or eliminating Alzheimer's disease and the other dementias.

A wide range of products have been tried in the treatment and or prevention of dementia – nootropics, psychotropics, neuroprotectors, hormone stimulators, antioxidants, anti-inflammatories, neurotransmitter enhancers etc.

The results of these trials have at times been disappointing or contradictory[2]. Whereas works continue on the development of possible amyloid inhibitors, at present, donepenzil, galantamine and rivastigmine seem to be the most popular cognitive enhancers, thought to act by inhibiting acetyl cholinesterase[3]. The effects of donepezil and rivastigmine have at best been modest for some patients and rather than reverse the process of dementia, they merely delay the rate and or onset of deterioration, with some questionable clinical benefit. The search for an ideal agents or agents that will completely reverse the dementing process continues.

In recent times herbal products have been advocated as having the potential to cure Alzheimer's disease. Herbal remedies have become very popular in medical practice, especially for chronic diseases (like dementia) that have defied tested orthodox cure. But no remedies can be properly endorsed without sound scientific evidence of potency, efficacy and safety. Walter and Rey4 reported that the most popular current psychiatric herbal drugs ("nerviness") include St. John's Wort, gingkobiloba and valeriana officialis.

The National Centre for Complementary and Alternative Medicine, in conjunction with the National Institute on Ageing, is testing the effect of Ginkgo biloba leaf extract, and some centers are already using the product[5]. In many developing countries like Nigeria, alternative medical practitioners have inundated the media with claims of discovery of native preparations (herbs, roots, fruits

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etc) that are capable of completely curing Alzheimer's disease and the other dementias.

One such product, Kippo comes from Japan. According to the manufacturers, Kippo is effective in controlling most old age diseases especially dementia. It is said to have been undergoing trials in Latin America, Canada, Germany, France, the Republic of Korea, with demonstrable efficacy and potency and no harmful side effects (Tanakan Miyabi, personal communication). We are not aware of its use in Africa, nor have we been able to locate any relevant literature on Kippo.

We therefore decided to do a clinical trial with this herbal product. In this paper, we present 4 case reports of our experience with Kippo in Nigerian dementia patients seen at our centre.

METHOD:

Study Site: The study was done at Nnamdi Azikiwe University Teaching Hospital, Nnewi (Eastern Nigeria). This is a 250 bed semi-urban tertiary health care and training institution providing medical services for about 3 million people in Anambra State, Eastern Nigeria.

SUBJECTS:

Four subjects whose family members consented to the study were recruited from the psychiatric outpatient clinic of the Hospital. The 10/66-dementia diagnostic procedure was adopted in identifying the subjects with dementia.

In summary, this involved the use of validated translated Igbo versions of the 10- word list learning test, the community screening instrument for Dementia (CSI – D) and the Geriatric Mental State interview schedule to evaluate each subject. Diagnosis of dementia was based on the ICD – 10 diagnostic criteria for research and the structured interview for diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementia of other aetiology (SIDAM). A responsible family member serving as the subject's principal carer gave verbal consent after the purpose of the investigation has been fully explained by the clinician.

Subjects with other co-morbid diseases were included if they were fit enough to participate in the interviews. All the subjects were permitted to continue their medications (anithypertensives, benzodiazepines or short term neuroleptics) but anti-cholinergics and any known cognitive enhancers either as drugs or food supplements were not allowed. Our institution's ethical committee approved the study.

PROCEDURE:

One of us (F.O.) carried out the efficacy measures without knowing what the subjects were receiving. A nursing sister separately dispensed the Kippo products to the subject's principal carer after the subject has been ascertained to have dementia by one of us (R.U). The subject's principal carer was asked to observe the subject closely at home and report any untoward development to the investigators. Efficacy assessment using the modified Nigerian version of the Mini Mental State Examination[6] and the dementia behaviour disturbance scale [7] was made at base line, 2 weeks, 4 weeks, 6 weeks and 8 weeks. The dementia behaviour disturbance scale (DBD) is designed to quantify observable behaviours usually associated with dementia through an interview with the patient's principal caregiver. The frequency of each of the 28 items of the scale during the preceding 2 weeks was rated by the subject's principal caregiver, using a likert – type scale where 0 = never, 1= rarely, 2 = sometimes, 3 = often and 4 = all the time. The total DBD score is the sum of the responses to the individual items (0-112), which is inversely proportional to the behavioural symptoms of the dementia subject.

The improvement subscale of the clinician's clinical Global Impression Scale (CGI) was used to rate the over all clinical assessment of improvement. This is a 7 – point scale ranging from very much improved (0) to very much worse (7). At each visit, the clinician (RU) rated the subject on the clinical Global Impression Scale (CGI) whereas the efficacy measures were blindly assessed by a separate person (F.O.)Any adverse effects reported by the subject's relative or observed by the clinician at any time was rated. Safety evaluations included physical examination at each visit and laboratory testing (blood, urine, faces, biochemical parameters) done at base line and at the end of the trial (week 8). After stopping Kippo at week 8, the CGI was again rated at week 10. The subject's principal carer administered the Kippo product at home. Fixed dosing was maintained for all the subjects at three Kippo packets every 24 hours throughout the study. Each Kippo packet contains powdered form of the herbal product, weighing about 5 grams.

The powdered Kippo was dissolved with ordinary water (either cold or warm) and swallowed by the subject under the supervision of the principal carer. The study period covered Dec. 2001 to March 2002.

CASE PRESENTATION

CASE 1

Mrs. R.O. a 72 year old menopausal widow and mother of 7 children was brought by her daughter for assessment. Her major symptoms were getting lost in the neighbourhood, asking of dead relatives, accusing children/grandchildren of stealing her personal effects and demanding to be taken home while in her house. These symptoms which had started 3 years

earlier, worsened some weeks before her presentation, with irritability, talkativeness and undue concern about security. Her blood pressure was 170/100mmHg; otherwise the physical examination was normal, with no focal neurological deficits. She was fully conscious and alert. Her scores on the validated Igbo version of Zaudig's SIDAM were: Orientation 80%, immediate recall 80%, short term memory 0%, long term memory 28.5%, intellectual abilities 20%, calculation 14.3% Hachinski 6, Rosen 4, construction 0%, apraxia 30%, total SISCO 34%, MMSE 40%, Expanded MMSE 37.5%. Her haematological and biochemical indices were normal. Following the 10-word list learning test, CS I-D and GMS interview, a diagnosis of dementia, probable multi-infarct with other mixed symptoms (ICD-10 DCR FO, 1.1. X 4) was made.
She was taking Nifedipine for her hypertension and occasional lorazepam or chlorpromazine for extreme restlessness/sleeplessness. She was recruited into the Kippo trial study on 5/12/2001. On the intake her DBD was 26, MMSE, 13. The protocol as already described was followed. She took 3 packets of Kippo daily.

The paired – test was used to compare her performance on the DBD and MMSE. After week 8 there was a statistically significant improvement in her DBD ($t = 8.75$, $P < .05$) but no change at all in her MMSE ($t=0$). Although she showed minimal improvement in her CGI at week 2, this showed minimal worsening at the 4th week. At week 10, her CGI again showed minimal worsening. . There were no observed side effects and her laboratory parameters remained normal at week 8.

CASE II

N.J. a 72 year old widower, retired farmer with no family history of memory or mental disorder, was brought for assessment by his son.
The main problems were asking to be taken home while at this own house, getting lost in the neighbourhood, inability to dress himself properly, poor self care. This was followed by embarrassing behaviour like being naked in the open without knowing, irrelevant talks, urinary and bowel incontinence and inability to remember his relation's names. A few weeks before assessment he was observed to be restless, disruptive and sleepless with nocturnal worsening of symptoms prompting his being brought to our unit. The initial symptoms were noted about 7 –8 months previously. He had pitting oedema and a blood pressure of 130/100mmHg and apart from non-specific T – abnormality on his ECG, his physical status was unremarkable. He was fully conscious and alert.

His scores on the SIDAM scale were as follows:- Orienation 10%, immediate recall 80%, short term memory 0%, long term memory 0%, intellectual abilities 0%, verbal and constructional abilities 0%, aphasia/apraxia 20%, SISCO 14.5%, MMSE 20%, EMMSE 17.5%,the Hachinski score was 06 and Rosen 05. The interview protocol was applied and a diagnosis of dementia (? Mixed multi-infarct and Alzheimers) was made. He was started on 3 packets of Kippo daily.

He was taking Zestril and frusemide for his hypertension and received occasional nitrazepam/chlorpromazine for extreme agitation/sleeplessness. His DBD and MMSE at intake were respectively 39 and 7. The paired t-test was used to compare his performance on the DBD and MMSE. While his DBD significantly worsened at week 8 ($t = 119$, $P>.50$), his MMSE significantly improved ($t = 4.7$, $P<.05$). His CGI improved at week 2 (CGI = 0) but dropped in week 6 and further in week 8. By week 10, his CGI had shown minimal improvement. There were no physical or laboratory adverse effects.

CASE III

E.B. a 74 year old widower has had his symptoms for the past 3 years. His son brought him for assessment on the basis of his getting lost in the neighourhood, wandering out of the house, and inability to recognize his children. The symptoms were very gradual in onset and showed nocturnal worsening. His blood pressure was 120/70mmHg and all the systems were physically unremarkable. Following the research protocol, a diagnosis of dementia was made (probable Alzheimer's). He was started on Kippo at the fixed dosage of 3 packets in 24 hours. One week thereafter, the son came to report that the patient had become more restless, sleepless and seemed generally confused. Though advised to bring the patient for re-evaluation, three months, neither the patient nor the family was seen again.

CASE IV

M.I. a 78 year old widow, mother of 5 with no family history of memory or mental disorder, was brought by 2 of her children for assessment. Her problem had lasted for a little over 8 years. The main symptoms were getting lost after going to church meetings, wandering out of the compound, poor grooming and inability to recognize her children. Three years previously she had been seen at a state psychiatric hospital (about 24 km from the study site) but did not continue any treatment. Her symptoms were gradual in onset, worsened at night and were progressive. Just before assessment she had developed bladder and bowel incontinence, slept poorly and was becoming difficult at home. Her physical status was unremarkable and she had a blood pressure of 120/80 mmHg. Following the study

protocol, a diagnosis of probable dementia in Alzheimer's disease was made. She was started on Kippo at 3 packets daily with nitrazepam when necessary. Unfortunately after recruitment and initial assessment, the patient/family was not seen again. After 3 months, this report was compiled without further analysis on the patient as no contact was possible.

DISCUSSION:

No meaningful conclusions can be made in grossly limited case reports such as we have presented here.

Although both of the two subject's who completed the study, received antihypertensives and other agents, there was no deliberate matching – an obvious disadvantage of non-randonised open label investigation. Interpretation of their differential responses is difficult. Whereas case one showed significant improvement on the dementia behaviour disturbance scale, case two demonstrated worsening on the scale following the use of Kippo. On the other hand, case 2 had improvement on the MMSE whereas case one showed no change at all on the MMSE. The performance of the 2 subjects on the efficacy measures would tend to suggest that the cognitive and behavioural/functional features of dementia may at times be independent. Thus behavioural disturbances may improve independently of cognitive functions, whereas cognitive improvement may not necessarily lead to improvement in behavioural disturbances.

The improvement of the DBD in case one and MMSE in case two noted in the second week, progressively decreased throughout the study period. The CGI followed the same pattern. This initial burst in behavioural and cognitive improvement for cases one and two respectively, may be due to non-specific factors. The enthusiasm of family members presenting their demented elderly relatives after distressful behavioural disturbances may contribute to apparent initial improvement. Indeed a number of studies have shown that placebo effects of antidementia drugs can result in both cognitive and behavioural improvement at the start of treatment[8]. Although ethical reasons would prevent the inclusion of placebo control groups in long term clinical trials, well conducted parallel group, cross over, placebo controlled antidementia drugs for upwards of 3-6 months could separate placebo from drug effects [24]. In this short report, we can not rule out apparent initial improvement (cognitive or behavioural) as a result of placebo effects in patients receiving proper orthodox assessment and care for the first time. Possible confounding effects of multiple drugs also need to be noted. Psychotropic drugs have been used in the management of behavioural and psychological symptoms of dementia at times with some beneficial effects on certain aspects of behaviour[8]. Both patients received psychotropic agents when necessary and this could influence their performance on the efficacy scales. Also in demented elderly patients with elevated blood pressure, antiphpertensives may have positive influence on cognition and behaviour[9]. Although some studies of the potential efficacy of antidementia agents have permitted the use of other drugs including antithypertensives and psychotropics, their possible effects on cognitive and behavioural features of dementia must be borne in mind.

If Kippo has any sustained beneficial effects on dementia, we are not able to say. As dementia is a devastating disease we thought it wise to try a new product which could potentially benefit the patients, without denying them known efficacious, safe therapy. Although our diagnosis of dementia was fairly rigorous, it is simply impossible to precisely identify Alzhemier's disease without tissue histology. Besides, we used the Kippo products for all the subjects irrespective of the dementia subtype. This was a serious weakness in our work. In a large number of subjects it would be more robust to separately evaluate the possible effects of Kippo on the different dementia subtypes with quantified severity.

In conclusion, we have demonstrated an initial improvement in behavioural disturbance following Kippo administration in one dementia patient and a worsening of the same parameter in another patient. There was also an improvement in cognitive performance in one patient and no change in the second patient. There was no reliable evidence for any adverse or toxic effects. The observed initial global improvement (CGI) was not sustained. We recommend large scale randomized, properly controlled study of the product before rejecting or accepting the claims of the manufacturers.

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