

THE CLINICAL EFFECT OF PENTOXIFYLLINE ("TRENAL") IN THE TREATMENT OF GERIATRIC PATIENTS

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INTRODUCTION

The increasing of life expectancy as the result of the progress of science, especially medical science, will increase the aged population group. James Coleman described in his book that by 1980, the United States expects to approximate 25 million of the aged, some 10 percent of the anticipated total population (Cobman, J.C., 1970). On other hand Freedman et al stated that in 1970 over 10 percent of the population was over 65 years old (Freedman, A.M., Kaplan, H.L., 1976) and Gross W. Meyer said that in 1969 the aged constituted 12 percent of the population (Mayer Gross., Slater & Roth 1970). In 1978 the total Indonesian population was 130 million. If 10 percent of this population were the aged, it means that there are 13 million of the aged in Indonesia. This population is too large to be forgotten. With our increasing longevity, mental disturbances in the aged have become increasingly important (Coleman, J.C., 1970). Busse, E.W. found that only 40% of the aged who live in community were free from psychological problems. Goldfarb stated that 50% of the geriatric institutional residents have severe psychiatric problems. Biological aging also brings a decline in physical strength and changes in physical appearance.

The vascular and nervous systems are among the first to suffer from the aging process. There is some degree of atrophy and a decrease in the number of neurons, fatty deposits form in the cerebral arteries, leading eventually to impaired cerebral circulation (Coleman, J.C., 1970). According to various authors, the most prominent psychiatric syndromes among the aged are senile brain disease and cerebral arteriosclerosis: Sheldon 65%; Bremer 60%; Syracuse 65%; Primrose 65%; Nielsen 65%; Kay 65%; and Mark 80% (Mayer Gross, Slater & Roth, 1970). Tyne in his study found that the percentage of senile dementia is as much as arteriosclerotic brain syndromes (Mayer Gross, Slater & Roth, 1970). It means such cerebral problem has much influence on the behaviour problem in the aged. We (the Indonesian psychiatrist) still believe that the most effective approach toward the psychiatric problem, including the geriatric problem, is a holistic approach that consists of the biological aspect, psychological aspect and sociological aspect (Setyonegoro, K, 1968). In this study, we will emphasize on the biological aspect in the treatment of geriatric patients.

It has long been believed that the vasodilator is the effective drug in the treatment of cerebral arteriosclerosis, especially when irreversible circulatory obstruction occurred, through supporting the compensatory mechanisms. Its compensatory mechanisms include the ability to develop collateral circulation, increase utilization of oxygen and reduce functional resistance beyond the obstruction. However the value of this treatment is questioned by many investigators, since vasodilators produced only a slight increase in circulation in some cases, and in majority of cases there was no change at all and sometimes even a marked reduction in circulation in the target area (Hess H., 1977, Schafer H.K., 1973). Muller, R., Lehrach and Grigoliet, H.G., stated that the development of a new preparation which was mainly based on the pharmacological principle of vasodilatation was in contrast to the present teaching of angiology. Furthermore they said that the site of action of vasodilators is the vascular muscle cell which is absent in the capillaries. Subsequently, capillary dilatation is not possible with vasodilators. And it is hard to imagine that the lumen of rigid arteriosclerotic vessels could be affected pharmacodynamically.

In addition, strong vasodilators frequently cause a reduction in systemic blood pressure and a steal effect, i.e., an excess of blood perfusion in the healthy area at the expense of blood perfusion in the diseased part. The preparation Trental, which was introduced into therapy in 1972, contains the xanthine derivative pentoxifylline (3, 7-dimethyl-1-(5-oxo-hexyl)-xanthine) synthesized in 1964.

In the treatment of circulatory disturbances, pentoxifylline can fulfil important preconditions of the new therapeutic principle developed by Ehrly. Pentoxifylline is capable of improving the flexibility of the erythrocytes (Muller, R., Lehrach, F., Grigoliet, H.G., 1975).

Other characteristics of pentoxifylline are (Lehrach, F., Muller, R., Theis. H., 1977; Muller, R et al., 1975; Hammer, O., Neuner, A., 1972):

1. The substance is freely soluble in water and lipids and can be used orally as well as parentally.
2. Pentoxifylline is almost completely eliminated in the form of metabolites via kidney.
3. Pentoxifylline exerts a mild vasodilating effect only and thus cannot be classified with the strong vasodilators.
4. Pentoxifylline produces a temporary clinico-therapeutic effect in areas with healthy vessels while in ischaemic areas it produces a long lasting effect. Rheographically pentoxifylline gives rise to a long lasting biphasic post-stenotic

increase in blood flow in a patient with vascular disease, phase I of which can be attributed to the initial vasorelaxation and phase II can be explained as increased perfusion of the impaired microcirculation and suggests a prolonged increase in the flow rate.

5. There are various mechanisms involved in the development of therapeutic efficacy of pentoxifylline i.e., in the promotion of the circulation and improvement of the nutrition of ischaemic tissues. The rheological effects which stand out clearly are of decisive importance for the areas with disturbed microcirculation.
6. Pentoxifylline produces an increase in stroke volume and cardiac output accompanied by a significant decrease in peripheral vascular resistance. The heart rate does not change significantly.
7. When used therapeutically even for a prolonged period of time pentoxifylline proved to be well tolerated, has no adverse effects on liver and kidney function, blood and coagulation status as could be observed in diagnostic laboratory tests.

There have been a number of reports stating that pentoxifylline is effective in treating patients with cerebral insufficiency. (Domingues et al, 1977; Lehrach, F. et al. 1975; Muller, R, et al, 1975; Denck, H, 1973). It was then decided to carry out a study in geriatric patients to evaluate the clinical effects of pentoxifylline in such cases. In the following we report our experiences in that study.

MATERIAL AND METHOD

There were 26 geriatric patients (6 males and 20 females) aged between 56 years and 89 years included in this open study. Twenty-one patients are residents of Panti Surya Geriatric Institution and the others are private patients. All patients are willing and able to participate this study. Each patient received 1 dragee of pentoxifylline (100mg active substance each) 3 times daily, for a period of 7 weeks in each case. If the patient was taking psychotropic drugs already, they were stopped before the study began, but antidiabetic medication was continued. Systematic psychotherapy was not performed during this study.

In order to detect any possible adverse effects, the following laboratory tests were performed before and after treatment: routine blood examination, liver function test, cholesterol and blood sugar test. We assessed the result of treatment through evaluation of the improvement of specific symptoms, side effects, tolerance and overall symptoms. The evaluation of the symptoms depend on:

- a. Psychiatric evaluation by a neurologist and psychiatrist.
- b. Daily observation by a staff member of geriatric institution for a resident of that institution or daily observation by the family of the patient in case of private patient.
- c. The information given by the patients concerning their subjective feeling.

RESULT

The patient characteristics are given in Table I. Although in this table the institutional patients were separated from the private, we did not compare the results of the groups since the number of the private patients was too small.

Agreement concerning the starting age for the geriatric person has not been concluded yet. 65 years is generally considered the beginning age for geriatric individual, but Ferraro (Arieti, S, 1969) chose 40 years. Goldfarb (Freedman, A.M., Kaplan, H.L., 1967) agreed that 65 years was the beginning age for the geriatric in general, but it could also occur in the younger case.

In our study the youngest patient was 56 years. He had been rejected by his family because his behaviour had become intolerable.

There is one private patient who suffered from diabetes and had been treated with 125mg chlorpropamide a day. Other concomitant illness mentioned in Table I remain untreated.

Table I: Reported Characteristics of Patients

Number of patients	Private patients — female : 5 — male : 0	Institutional patients — female : 15 — male : 6	Total — Female : 20 — male : 6
Age	60 yr — 80 yr \bar{X} = 68,4 years	56 yr — 89 yr \bar{X} = 74,5 years	56 yr — 89 yr \bar{X} = 63,37 yr.
General parameters	Blood pressure systolic diastolic pulse rate	135 mmHg — 195 mmHg 60 mmHg — 100mmHg 60 — 114/minute	(\bar{X} = 144mmHg.) (\bar{X} = 80.9mmHg.) (\bar{X} = 84,6/min.)
Concomitant illness	Diabetes: 1; Hypertension : 12 Parkinsonism : 1; Paraesthesia : 4 Low back pain : 1; Haemorrhoids : 1		

Most of the specific symptoms were alleviated in more than 56% of cases, except for introversion (30%) and reduced visual field (32%). Furthermore pentoxifylline was ineffective in 5 cases of introversion (70%), 3 cases of mental unrest (30%) and 4 cases of loss of affect and unhappy (29%). One case each of introversion, mental unrest and loss of affect became worse. Additionally a case of loss of work capacity became worse after pentoxifylline treatment. All of vertigo cases and apathy cases (100%) were cured and it appears that for both these symptoms, pentoxifylline is more effective (Table II).

Table II: The Result of Pentoxifylline Therapy on Specific Symptoms

Symptom	No. of Patient	Result			
		Good	Improved	Unchanged	Worse
Vertigo	20	14 (70%)	6 (30%)	—	—
Headache	19	13 (68%)	4 (21%)	2 (10%)	—
Sleep disturbances	17	11 (64%)	3 (17%)	3 (17%)	—
Memory loss	20	12 (60%)	4 (20%)	4 (20%)	—
Loss of mental drive	17	7 (42%)	3 (17%)	7 (42%)	—
Word finding difficulty	13	8 (61%)	—	5 (39%)	—
Loss of concentration	19	9 (47%)	3 (15%)	7 (36%)	—
Easy tiring	21	11 (52%)	5 (24%)	5 (24%)	—
Loss of initiative	16	6 (37%)	3 (19%)	7 (44%)	—
Loss of work capacity	17	8 (47%)	5 (29%)	3 (17%)	1 (7%)
Loss of social contact	16	10 (62%)	4 (25%)	2 (13%)	—
Loss of tolerance (participation)	14	7 (50%)	3 (21%)	4 (29%)	—
Negative feeling	6	3 (50%)	2 (33%)	1 (17%)	—
Apathy	6	5 (83%)	1 (17%)	—	—
Introversion	7	2 (30%)	—	4 (56%)	1 (14%)
Mental unrest	10	7 (70%)	—	2 (20%)	1 (10%)
Loss of affect and unhappy	14	7 (50%)	3 (21%)	3 (21%)	1 (8%)
Tinnitus	15	5 (33%)	5 (33%)	5 (33%)	—
Reduced visual field	12	2 (16%)	2 (16%)	8 (68%)	—

Table III indicates that 23% (6 cases) of the patients had excellent results, 26.9% (7 cases) of patients good results, 30.7% (8 cases) of the patients showed improved result and 19.2% (5 cases) of the patients remained unchanged. None of the patients showed a worse result. It can thus be reported that more than 80% showed clinical improvement after 7 weeks pentoxifylline treatment.

Table III: The Overall Assessment Effectiveness of Pentoxifylline

Effectiveness	Excellent	Good	Improved	Unchanged	Worse
No. of patients	6	7	8	5	—
Percentage	23%	26.9%	30.7%	19.2%	0%

There was no serious side effect in more than 88% of the patients (Table IV) and only 11.5% of the patients showed poor tolerance toward pentoxifylline. No severe side effect occurred during this study, to warrant premature termination of therapy. In our view the trial design might have influenced the figure of good drug tolerance. For example severe heart disease patients are excluded from the sample and the dose used in this study was lower than others.

Table IV: Patient Tolerance toward Pentoxifylline

Tolerance	Good	Moderate	Poor	Bad
No. of patients	14	9	3	—
Percentage	53.8%	34.6%	11.5%	0%

Details of the side-effects observed are given in Table V. There is no effect of pentoxifylline on blood pressure. Giddiness occurred in the first day for 23% of the patients but did not need special treatment and it ceased the day after. Congestion in the head occurred in the first day for 7.6% (2 cases) of patients but it did not disturb the patients too much. Gastric irritation occurred in 15.3% (4 cases) of the patients. Antacid was needed in 3 of the cases. The drug should not be given on an empty stomach. It was not necessary in any case to discontinue the drug. Other side effects (flushing, burning face, hyperhidrosis) occurred in 11.4% (3 cases) of the patients but no special intervention was needed.

Table V: The Side Effects of Pentoxifylline

Side Effect	No. of Patients	Percentage
Giddiness	6	23
Congestion in head	2	7.6
Gastric irritation	4	15.3
Others	3	11.4
Blood pressure	0	0

LABORATORY ASSESSMENT

Laboratory tests revealed no harmful effect. This result is in agreement with other investigators (Buckert, D; Harwart, D, 1976; Denck, H, 1973; Hammer, O; Neuner, a, 1972; Lehrach, F et al 1977; Schafe, H.K., 1973). Dominguez et al 1977 reported significant reduction in cholesterol levels was recorded in their study, but our study did not confirm their finding. Liver function, renal function, cholesterol level and blood sugar level remained unchanged.

DISCUSSION

Schafe, H.K., 1973 and Dominguez et al 1977 stated that it is difficult to obtain objective results in the aged with cerebrovascular insufficiency. Furthermore the open method, that we have used in this study, has the element of subjectiveness. In order to reduce bias we have arranged our method of study thus:

- a. Organisation : To separate clearly between the data collector and the data analyst.
- b. Evaluation : Information for inclusion in evaluations depend on more than one person. We solve differences in information through mutual discussion.

Kopenhagen K, Wenig H.G, Muller R and Denck H concluded that clinical therapeutic studies have provided evidence to suggest that administration of pentoxifylline improves clinical symptoms in patients with cerebrovascular insufficiency. Our results are in agreement with those reported by Denck H and Kopenhagen et al.

Schafe, H.K. reported that 92% of the cases showed important changes and Buckert, D and Harwart D (1976) reported a higher percentage (96% of the cases) of success.

Our study produced a lower percentage of cases who showed clinical improvement after pentoxifylline treatment (80%). The explanation of this difference may lie in

- a) Dosage: Lehrach F, Muller R and Theis H stated that the dosage of preparation recommended depended on the severity of the circulatory disorder. In circulatory disorders of a milder degree oral administration of 3 x 1-2 dragees of 100mg daily proved sufficiently effective. In severe forms of the disease, parenteral or combined parenteral and oral administration proved necessary. The dose used in our study was very low: 100mg pentoxifylline 3 times daily. Schafe H.K. used 100mg pentoxifylline 3-4 times per day as the average oral dosage and intravenous or intra-arterial injection of 100-200mg of pentoxifylline in severe stages. Each patient in the study of Buckert D and Harwart D received 2 dragees of pentoxifylline (100mg active substance, 3 times daily).

- b) Duration of treatment:

Schafe, M.K. stated that the duration of therapy obviously played a decisive role in the responsiveness of cerebrovascular symptoms. The decisive change towards the disappearance of symptoms such as headache, dizziness, insomnia and emotional instability occurred only after prolonged treatment. The duration of treatment in our study is shorter than other investigators (Schafe M.K.: 3 months, Buckert & Harwart: 8 weeks).

Lehrach F, Muller R and Theis H (1977) concluded that undesirable side effects were usually gastrointestinal discomfort (stomach complaints, sensation of fullness, nausea). Vertigo, congestion in head and palpitations were occasionally registered especially after parenteral administration. It was necessary to discontinue the preparation in 1.2% of the cases. Giddiness is the most frequent side effect in our study and the next is gastric irritation. It was not necessary to discontinue the preparation since the side effects were mild or it could be overcome by special intervention.

Table II showed that pentoxifylline is less effective in the treatment of the reduced visual field symptom than other specific symptoms. It does not mean that this is against the Lehrach F, et al (1977) statement, the Trental® proved to be effective in circulatory disorders of the fundus of the eye and that long term oral Trental therapy had a favourable effect on chronic conditions of the retina (arteriosclerotic chorio-retinopathy). In our cases, we are not sure that this specific symptom (reduced visual field) is caused by circulatory disturbances. The chronicity of the disease obviously played a decisive role in this situation. The therapeutic value of the so-called vasodilators is often placed in doubt because of their effect on haemodynamics and because their experimental clinical use has not always resulted in objectively satisfactory effects. On the other hand a new therapeutic principle has been introduced. Muller H, Lehrach F and Grigoleit H.G. (1975) concluded that the proved therapeutic efficacy of pentoxifylline in cases of circulatory disturbances confirms that the new therapeutic principle is correct and clinically practicable. Whether the action of pentoxifylline corroborates and fulfils the essential preconditions of new therapeutic principle or not, is a matter for scientific discussion. The important point for the practising clinician is the positive effect on clinical findings and for the patient, it is the subjective change in his condition.

SUMMARY

3,7-dimethyl-1-(5-oxohexyl) xanthine (pentoxifylline, Trental®) was given orally to 26 patients (56 years — 89 years). Each patient was treated with 100mg pentoxifylline 3 times per day for 7 weeks and then we assessed the result of the treatment through evaluation of the improvement of the specific symptoms, side effects, tolerance and overall symptoms. Definite improvement was noted in 21 cases (80.1%). There was no evidence of significant side-effects from the preparation, either subjectively or in objective laboratory tests.

On the basis of these findings, it may be said that pentoxifylline is effective in overcoming mental disturbances in the aged without significant side effects. A further study using a double blind method and larger number of cases is needed.

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