

## 22. *Treatment of Amyotrophic Lateral Sclerosis with Phthalazinol, a Cyclic AMP Phosphodiesterase Inhibitor*

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Amyotrophic lateral sclerosis is today a fatal disorder due to the relentlessly progressing muscular atrophy. Neither the cause, nor the treatment has been known for this disease.<sup>1)</sup>

However, the recent observation<sup>2)</sup> of affected muscles of this condition revealed a significant low basal activity of adenylyl cyclase of the muscles. Cyclic AMP, produced by adenylyl cyclase, has been known to be an essential factor in glycogenolysis, lipolysis, and myoglobin-biosynthesis and also in the synaptic release of acetylcholine.<sup>1)</sup> Such evidences led us to try phthalazinol, a potent cyclic AMP phosphodiesterase inhibitor, in the treatment of 9 patients suffering from this disease and the clinical aspects of this observation have been subjected to the publication.

**Patients.** Three female patients aged 49, 59 and 78 years and 6 male patients 43, 43, 48, 51, 54, and 59 years were subjected to the trial. The duration of disease after the onset of symptom amounts 6, 2, and 1 years respectively in the female cases and 5, 3.5, 3, 2, 2, and 10 years respectively in the male patients and all patients were severe, and 4 patients were unable to walk and were keeping bed. One female patient aged 78 years had dyspnea and oxygen inhalation was continued since 6 months ago. All patients had dysphagia with various severity, besides the typical involvement of the muscles with the characteristic distribution and progression. All patients had a vocal weakness and a difficulty in speech with various degree and two patients could not speak.

All patients received various types of treatment, but their muscular atrophy and weakness were rapidly progressing.

**Clinical trial of phthalazinol treatment.** After the routine clinical and laboratory examinations, the administration of phthalazinol was started under the open study and the observation has been continued every week, mainly in the out patients department, except 2 hospitalized patients. The measurement of cyclic AMP level<sup>4)</sup> of the blood and the spinal fluid was performed by Gilman's method

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modified by us in one female patient aged 48 years before and one month after phthalazinol treatment with a daily dose of 1.2 g.

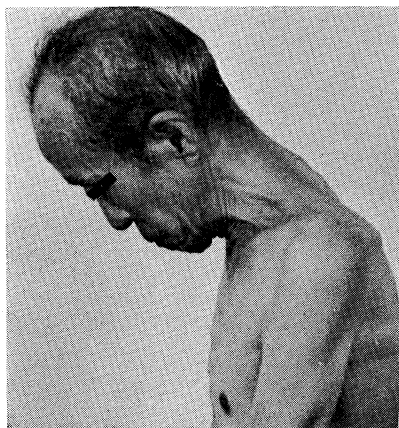
The daily dose of phthalazinol was 600 mg in the start and was elevated to 900 mg and finally that of 1.2 g (roughly 20 mg/kg) of phthalazinol has been continued since 8 months before. Phthalazinol (7-ethoxycarbonyl - 6,8 - dimethyl-4-hydroxymethyl-1 (2H)-phthalazinone) was synthesized by Shimamoto and Ishikawa in order to elevate cyclic AMP in atheromatous lesions and it was found that phthalazinol strikingly enhances the regression of experimental atherosclerosis of cholesterol-fed rabbits. This compound shows a highly potent cyclic AMP phosphodiesterase inhibiting activity in vitro and in vivo in various tissues of man and animals. The compound used was produced by Banyu Co., Ltd.

**Results.** The response of patients to a low dose of phthalazinol was not clear and a definite progression of muscular atrophy continued further in four patients despite the treatment, but that to a high dose, the daily administration of 1.2 gm of this compound, was quite clear almost in all patients definitely retarding and often stopping the further progression of muscular atrophy for the past 3 to 6 months. The most common initial response was the increase in the intensity of voice and the improvement of dysphagia and expectoration. A slight, but definite increase in the muscular strength was often recognized in mildly to moderately affected muscles, but not in severely affected muscles. A slight but a definite recovery from atrophy was also shown in some of slightly or moderately affected muscles.

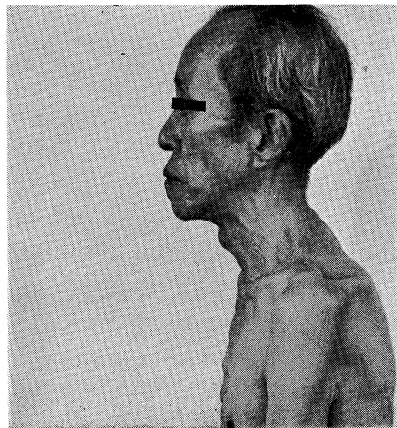
In one female patient aged 78 years kept under oxygen inhalation, the respiration improved quite rapidly after initiation of the medication and it made her unnecessary to inhale continuously oxygen. The expectoration became markedly easier and improved and her voice became louder, but the muscle strength of her extremities did not appreciably increase.

The most dramatic improvement was observed in one male patient aged 59 years, who could not support his head because of the weakness of neck muscles. After one month of daily administration of 1.2 gm of phthalazinol, he began to elevate, move and support his head as shown in photo 1. Another male patient aged 51 years, who could not elevate 1 kg of bottle by his both hands, began to elevate the bottle to his eye-level one month after the treatment and he also gained the muscle strength in his hands as shown in Photo 2. The improvement of these patients is still continuing during the 2 and 4 months of the treatment.

The concentration of plasma cyclic AMP level was slightly increased on phthalazinol (1.2 g daily) from 7 pmol/ml to 11.0-13.5

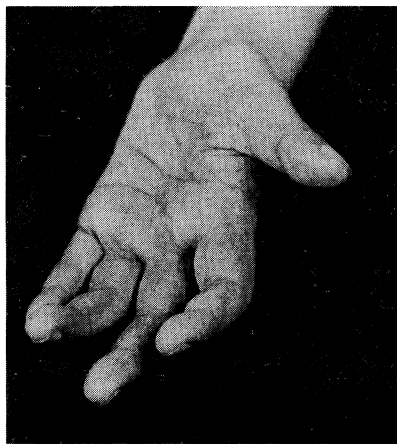


A



B

Photo 1. Fifty nine years old patient with 10 years of history could not support his head since thirteen months before phthalazinol-treatment. (A) After one month of the treatment, he began to elevate and support his head. (B)



A



B

Photo 2. Fifty one years old male patient with 2 years of history could not extend his fingers since one year before phthalazinol treatment. (A) After one month of the treatment, he began almost perfectly to extend his fingers. (B)

pmol/ml in one patient and the concentration of cyclic AMP in spinal fluid was also increased from 4.2 pmol/ml to 7.1 pmol/ml.

No side effect was observed in the clinical and laboratory examinations.

**Discussion.** According to the personal communication, Prof. T. Takemi (1975)<sup>1)</sup> treated one patient suffering from this disease

in a daily dose of 600 mg of phthalazinol and obtained a favorable result and similar favorable response was also obtained in 2 patients by Prof. T. Miyamura. In this observation, we could obtain a similar favorable response in our 9 patients using a relatively large daily dose of phthalazinol.

According to the report from Profs. W. King Engel and B. R. Brooks et al. (1975),<sup>5)</sup> they found a profound low level of cyclic AMP in the spinal fluid of the patients suffering from amyotrophic lateral sclerosis ( $P=0.0005$ ). They also observed that the administration of phthalazinol significantly increased and restored the cyclic AMP level of spinal fluid of their patients in a dose dependent manner, accompanied by an increase in the strength of their affected muscles by phthalazinol (20–50 mg/kg, daily) without any side effect.

The lack of recognizable side effect and the favorable effect of phthalazinol treatment shown in this trial may suggest the importance of further research on the treatment with phthalazinol of this hitherto desperate condition.

**Summary.** The administration of phthalazinol, in a daily dose of 1.2 g or 20 mg/kg, has been shown to retard or to stop the progression of their muscle atrophy, at least for 3 to 6 months of the present observation period, in all 9 patients suffering from hitherto desperate condition of amyotrophic lateral sclerosis without recognizable side effect. Two patients exhibited a marked increase in the strength of their moderately affected muscles.

### References

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