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34. Ryuichi Kimura,* Masanao Ogawa, and Takahiro Yabuuchi** : Studies on Thiophene Derivatives. III.*** Clinical Application of 3-Piperidino-1,1-di(2-thienyl)-1-butene as a New Antitussive.

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The antitussive effect of *dl*-3-piperidino-1,1-di(2-thienyl)-1-butene hydrochloride (*dl*-PBN) has been demonstrated by Kasé.[1] According to his work, it was estimated that the antitussive effect of *dl*-PBN in dog was about 1.5 times that of morphine, about 1.8 times that of Methadone, and about 4 times that of *dl*-3-dimethylamino-1,1-di(2-thienyl)-1-butene hydrochloride. The lethal dose of *dl*-PBN was about 1/6 of that of morphine and 1~3 times that of Methadone in mice, rats, and dogs. Consequently, the therapeutic index, LD_{50}/ATD_{50}, of its antitussive action was larger than that of Methadone.

The optical resolution of *dl*-PBN was carried out in this laboratory and it has been estimated by Fujimura that the pharmacological effect of *d*-PBN was stronger than that of *dl*-PBN in mice and dogs, and that the effect of *l*-PBN was weaker than that of *dl*-PBN.

Furthermore, *dl*-PBN did not show any emesis or anorexia, and the degree of hypnosis and salivation in dogs was much less than those caused by morphine or Methadone. Continued daily dose of 1.0 mg./kg. of *dl*-PBN by intravenous injection in dogs for 20 days had indicated that there was neither acute tolerance nor cumulative action of the antitussive effect.[1]

dl-PBN and *d*-PBN seemed to be a promising new antitussive drugs from the pharmacological properties mentioned above, further studies on the antitussive effect and safety dose in patients were madə, and several findings are reported here.

dl-PBN was obtained as white crystals of m.p. 189~190° and tablets containing 1 mg. of *dl*-PBN in each tablet were employed for oral use in 113 patients who required antitussive medication. The degree of relief obtained, i.e. reduction in frequency, intensity, and after-effect of coughing, as estimated by the medical and nursing staff, was classified into four categories, i.e., no relief, slight relief, moderate relief, and marked to complete relief. The results obtained are summarized in Table I.

Table I. Antitussive Effect from Various Doses of *dl*-PBN

Diagnosis		Pulmonary tuberculosis			Bronchitis
Group		I	II	III	IV
		Dosage			
Degree of relief	Total No. of patients	2 mg./day *dl*-PBN	4 mg./day *dl*-PBN	3 mg.×3/day *dl*-PBN	2 mg./day *dl*-PBN
None	17 (15.0%)	7 (26.9%)	1 (12.5%)	2 (20.0%)	7 (10.1%)
Slight	34 (30.1%)	10 (38.4%)	2 (25.0%)	2 (20.0%)	20 (29.0%)
Moderate	34 (30.1%)	6 (23.2%)	3 (37.5%)	5 (50.0%)	20 (29.0%)
Marked	28 (24.8%)	3 (11.5%)	2 (25.0%)	1 (10.0%)	22 (31.9%)
Total	113	26	8	10	69

The total 113 cases were divided into four groups, I, II, III, and IV, according to diagnosis and by medication. The patients with pulmonary tuberculosis in group I and those with bronchitis in group IV received one daily dose of 2 mg. of *dl*-PBN and

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1) Y. Kasé, *et al.* : This Bulletin, **3**, 394(1955).

the patients with pulmonary tuberculosis in group II were treated with one daily dose of 4 mg. of *dl*-PBN. Appearance of the effect occurred in 30~60 minutes after administration and the duration of effect lasted for 2~4 hours. It was observed that viscosity of the sputum decreased and expectoration became easier. The patients in which no relief was obtained had heavy sputa, due to new focus or large cavity. The patients in group III received three doses of 3 mg. of *dl*-PBN daily. In oder to estimate any effect of *dl*-PBN on the hematopoietic system or on renal functions, 3 patients in group III were given the dose for 90 days in this study, receiving a total of 810 mg., but there was no evidence of toxicity from *dl*-PBN on the hematopoietic system or on the renal function at the dose level given in Table I. There was no evidence of development of tolerance to *dl*-PBN or of addiction even in patients who received it over a prolonged period. As a side effect attributable to this compound, dry lips was recorded in 5 patients but constipation, which is known to be the side effect of codeine, was not observed.

The antitussive effect of *dl*-PBN and *d*-PBN was then evaluated by comparison with codeine in clinical application. Thus, 32 patients with persistent cough were selected from the population of Kyoto National Sanatorium. They had not received a prolonged administration of codeine before this study. Three materials, 6 mg. of *dl*-PBN, 3 mg. of *d*-PBN, and 20 mg. of codeine phosphate, were supplied in tablets of identical appearence and were given 3 times a day during 5 days each, with cross-over. In the first week, one patient would be treated with 3 mg. of *d*-PBN for 5 days and in the following 2 days he was not treated with any antitussive. In the second week, he would be treated with 6 mg. of *dl*-PBN in the same manner and in the third week, similarly with codeine phosphate. The degree of relief of coughing estimated by the medical staff was classified into the same four categories and the result is summarized in Table II.

Table II. Antitussive Effect of *dl*-PBN, *d*-PBN, and Codeine Phosphate

Degree of relief	Dosage		
	6-mg. doses of *dl*-PBN	3-mg. doses of *d*-PBN	20-mg. doses of codeine phsophate
None	10 (31.2%)	11 (34.4%)	9 (28.1%)
Slight	17 (53.2%)	13 (40.6%)	17 (53.2%)
Moderate	3 (9.4%)	4 (12.5%)	4 (12.5%)
Marked	2 (6.2%)	4 (12.5%)	2 (6.2%)
Total No. of patients	32	32	32

No great difference was found in the antitussive effect of 6 mg. of *dl*-PBN, 3 mg. of *d*-PBN, and 20 mg. of codeine phosphate. It was seen that the antitussive effect of 3 mg. of *d*-PBN and 20 mg. of codeine phosphate was approximately the same, while that of *dl*-PBN was slightly less than 1/2 of that of *d*-PBN.

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