Antitussive Activity of the N-Oxides of Opium Alkaloids

Since two years ago we have been studying the antitussive action of the N-oxides of opium alkaloids. Recently, the antitussive action of the N-oxides of dihydromorphine, morphine, and dihydrohydroxycodine was reported by Kelentey, *et al.*¹⁾ This hastened us to publish our results briefly here.

The method used for producing cough in animals was as follows.

(A) Chemical Stimulus: A guinea pig was placed in a desiccator and allowed to inhale SO₂-containing air for one minute, then the animal was placed in open air, and the number of coughs for 5 minutes was observed.

(B) Mechanical Stimulus: A guinea pig was anesthetized lightly by intraperitoneal injection of 15 mg./kg. of pentobarbital sodium and fixed in a dorsal position. The trachea was exposed and a small hole was cut in it. When a stimulating hair, was introduced through the hole, for about 3 cm., a violent coughing was evoked. The stimuli were given at 15, 30, 60, 90, and 120 mins. after the injection of a drug. One animal can be used several times repeatedly with a rest interval of 10 or more days.

In both methods even the presence of one cough response was thought as ineffective and ED₅₀ was calculated by the up-and-down method.²⁾ The results are summarized in Table I.

TABLE I. Antitussive Activity of Opium Alkaloids and their N-Oxides
ED₅₀ (mg./kg.) in guinea pigs

	Codeine		Morphine		Dihydrocodeine		Dihydromorphine		Narcotine Base
	Phosphate	N-Oxide	HCl	N-Oxide	Phosphate	N-Oxide	HCl	N-Oxide	
A method	14.4	1.02	5.90	3.34	3.21	—	5.01	6.95	41.4
B method	18.4	11.3	6.40	5.01	5.01	48.7	3.93	6.40	44.9

We studied mainly the pharmacological actions of codeine N-oxide, which, by intravenous injection of 15 or 26 mg., did not change the carotid blood pressure and respiration of a cat anesthetized with urethan (1 g./kg., subcutaneously). Morphine hydrochloride and codeine phosphate lowered the blood pressure and depressed the respiration seriously in the same doses. Codeine N-oxide elevated the pain-threshold of pressure on mouse tail³⁾ only to 70% by subcutaneous injection of 200 mg./kg. On the contrary, codeine phosphate resulted in an elevation of 120% of the pain-threshold at 50 mg./kg.

Acute toxicity of codeine N-oxide was very low. It was about 1/6 of codeine phosphate intravenously and 1/4 by oral administration. In clinical trials, codeine N-oxide is twice as effective as codeine phosphate and does not give any side effects.

We wish to express our thanks to Drs. Nishizawa and Takahashi of Takeda Pharm. Ind., Ltd. for supplying the drug preparations.

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December 14, 1957.

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