Prolonged Antitussive Action of a Resin-Bound Noscapine Preparation

By OLE WULFF

The prolongation of the antitussive effect of resin-bound noscapine has been examined by means of experimentally induced cough in guinea pigs. The paper also includes a comparative study of the antitussive effect of noscapine and codeine.

THE ANTITUSSIVE effect of noscapine (formerly called narcotine) was discovered in animal experiments, and the observation was confirmed from many sources. Table I summarizes some of the animal and human experiments showing this special effect of noscapine compared with codeine.

The antitussive effect of noscapine only lasts for 2–4 hr. For this reason, it is desirable to obtain a preparation with a prolonged effect in order to allow patients to sleep. For this purpose, noscapine was bound to a suitable ion exchange resin. The Dowex 50[1] (200–400 mesh) with 4% cross linkage was found to give a product with satisfactory prolonged action. The preparation[2] contains 62–64% of noscapine. The resulting noscapine compound can be eluted *in vitro* by treatment with an ion-containing solution, such as artificial gastric fluid or artificial intestinal fluid. The elution rate was found to be almost independent of pH and temperature and not influenced by enzymes. In recent years resin complexes with many alkaloids have been made and described. For references see, *i.e.*, Smith *et al.* (7). However, very few *in vivo* experiments have been conducted. This paper reports the results of experiments which show the delayed effect of resin-bound noscapine in animals.

METHODS

The preparation has been tested on experimentally produced cough in guinea pigs. The method described by Friebel *et al.* (3) was used, although with a few modifications.

Guinea pigs, 300–700 Gm., were placed in a jar and exposed to a mixture of 0.1% sulfur dioxide in atmospheric air for 3 min. The guinea pigs rarely coughed during the exposure, but coughing was observed when they were taken out of the sulfur dioxide-containing atmosphere. The number of coughs was counted during a period of exactly 2 min. after placing the experimental animals in sulfur dioxide-free air. The number of coughs varied greatly from animal to animal, but was found to be relatively constant from time to time in the same animal, especially when the animals were tested several times during the same day, as seen from the control groups in Table III. In the morning, the animals were tested for cough sensitivity as described above. Animals which did not cough during the control tests were discarded; the remaining animals were given the test substances orally in sugar syrup with a graduated syringe. The tip of the syringe was introduced into the mouth of the animal, and by depressing the plunger slowly, a well-defined amount of the substance could be administered. The animals readily took the syrup. The control animals were given 0.5 ml. of syrup. By means of this test, the duration of the antitussive effect of noscapine chloride was compared with that of resin-bound noscapine.

RESULTS

In one series, tests were carried out 1.5 hr., 3.5 hr., and 7 hr. after administration of the compounds to be tested. In a second series, tests were carried out 3 and 5 hr. after administration of the above compounds. Tables II and III show the average initial number of cough attacks and the average decrease in number of cough attacks.

The P values in Tables II and III refer to the t test ($t = m/s.e.m.$), where m (the mean decrease) and the standard error of the mean are calculated from the difference in cough numbers for each animal. These values show that the animals had a consistent decrease in the number of cough attacks after the administration of noscapine and the noscapine-resin complex, respectively. But they show also that the decrease in cough attacks is observed over a longer period after the administration of resin-bound noscapine than after the administration of noscapine chloride.

As a control of the efficacy of the method, the effect of codeine phosphate and noscapine chloride has been compared. Of a total number of 115 guinea pigs, 59 were given codeine phosphate and 56 noscapine chloride. The animals were injected intraperitoneally with a 2% solution of the compound 30 min. before each test. The test was repeated three times with each animal at intervals of several days, so that saline and the large and

TABLE I.—ANTITUSSIVE EFFECT OF NOSCAPINE AND CODEINE

Ref.	Stimulation	Isodynamic Doses, mg./Kg. Codeine	Noscapine
(6)	Cats, mechanical stimulation of trachea's mucosa	0.5–1	0.5–1
(1)	Humans, inhalation of citric acid-aerosol	30	5–15
(5)	Cats, electrical stimulation of n. laryngeus after technique by Domenjoz (2)	3	3
(4)	Dogs, cats, mechanical stimulation. Guinea pigs, stimulation by means of sulfur dioxide	4	30
(9)	Guinea pigs, injection of rabbit antiserum	2	2

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[1] Trade name for the series of sulfonic acid cation exchange resins marketed by the Dow Chemical Co.

[2] Marketed as Longatin.

TABLE II.—ANTITUSSIVE EFFECT OF NOSCAPINE HYDROCHLORIDE COMPARED WITH NOSCAPINE–RESIN

	Initial No. of Cough Attacks	Av. Decrease (No. of Cough Attacks) After 1.5 hr.	P	3.5 hr.	P	7 hr.	P
Noscapine hydrochloride, 10 mg./Kg., n = 20	3.30	1.30	<0.05	0.55	>0.4	0.55	>0.4
Noscapine-resin corresponding to 10 mg./Kg., n = 21	3.62	1.86	<0.01	1.38	<0.05	0.71	>0.2
Controls, n (×3) = 19	3.05	0.53	>0.2	0.32	>0.4	0.37	>0.4

TABLE III.—ANTITUSSIVE EFFECT OF NOSCAPINE HYDROCHLORIDE COMPARED WITH NOSCAPINE–RESIN

	Initial No. of Cough Attacks	Av. Decrease (No. of Cough Attacks) After 3 hr.	P	5 hr.	P
Noscapine hydrochloride, 10 mg./Kg., n (×3) = 12	3.75	0.17	>0.6	0.33	>0.6
Noscapine-resin corresponding to 10 mg./Kg., n (×3) = 12	4.33	1.25	<0.02	1.50	<0.05
Controls, n (×3) = 10	2.80	0.40	>0.4	0.30	>0.6

small doses of the compound were given in random succession which had been decided upon in advance. Saline was given in one experiment, and the large and small doses of the compound to be tested were given in two other experiments.

In this way each animal acted as its own control. The experimental results were statistically analyzed in the same way as indicated above. The results are shown in Table IV. This table shows that the antitussive effect of noscapine is to equal that of codeine.

DISCUSSION

As it appears from Tables II and III, there is a significant reduction in the number of cough attacks in the experimental animals 5 hr. after the administration of resin-bound noscapine, while the effect of the noscapine hydrochloride wears off 1.5 to 3 hr. after the administration.

Experiments conducted by Vedsø (8) show that only oral administration of noscapine hydrochloride in divided doses spread over 2.5 hr. will produce a blood concentration curve similar to that obtained after a single administration of the resin-bound noscapine present in Longatin. The blood concentration curves indicate a rapid disappearance from the plasma with an apparent quick deposit in the tissues. The cough experiments reported here with the guinea pigs imply that the retardation in the release of noscapine from the resin and the resulting retarded absorption from the alimentary tract also creates a prolonged antitussive effect.

The cough experiments dealt with in this article were performed before Vedsø (8) worked out his analytical technique and compared the resin-bound noscapine with noscapine chloride. Therefore, the cough experiments do not include blood analyses of noscapine, nor do they include a comparison between the antitussive effect of noscapine given in a single dose and in divided doses. This experiment might have elucidated whether the prolongation observed in the blood concentration after the administration of noscapine chloride in divided doses also would appear to produce retardation of the antitussive effect.

SUMMARY

After oral administration of resin-bound noscapine and noscapine chloride, the duration of the antitussive effect of the two compounds is compared by means of experimentally induced cough in guinea pigs.

A considerable prolongation of the effect of noscapine was observed when administered resin-bound.

The antitussive effects of noscapine hydrochloride and codeine phosphate, respectively, have been compared after intraperitoneal injection in guinea pigs. In accordance with the literature, the two substances, milligram for milligram, appeared to have the same effect.

TABLE IV.—COMPARISON BETWEEN THE ANTITUSSIVE EFFECT OF NOSCAPINE HYDROCHLORIDE AND CODEINE PHOSPHATE IN GUINEA PIG

	Av. of Control Tests (No. of Cough Attacks)	Av. Decrease (No. of Cough Attacks)	P
Noscapine hydrochloride, 5 mg./Kg. i.p., n(×4) = 56	4.46	0.77	<0.1
Noscapine hydrochloride, 10 mg./Kg. i.p., n(×4) = 56		1.65	<0.002
Codeine phosphate, 5 mg./Kg. i.p., n(×4) = 59	3.37	0.89	<0.05
Codeine phosphate, 10 mg./Kg. i.p., n(×4) = 59		1.83	<0.001

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Phytochemical Studies of Egyptian *Plantago* Species (Glucides)

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Mucilages are isolated from the seeds of eight Egyptian *Plantago* species by extraction with cold and hot water successively. The percentages, physical properties, as well as the qualitative and quantitative determinations of the sugar components of the different mucilage fractions are reported. The mono- and oligosaccharides identified in the seeds are planteose, planteobiose, sucrose, D-glucose, L-fructose, D-xylose, and L-rhamnose. The qualitative and quantitative determinations of the glucoside aucubin in the seeds are carried out.

THERE ARE 21 species of plantain in Egypt; some are very rare while others are common, particularly *Plantago albicans*, *P. ovata*, *P. major*, and *P. crypsoides*. *P. albicans* grows abundantly in the western Mediterranean regions. The majority of these *Plantago* species show xeromorphic characteristics, growing in deserts under severe conditions of drought.

The present work studies the glucides of the most common Egyptian *Plantago* species.

EXPERIMENTAL

Materials

P. notata.—Plants collected in April 1962 from Burg El Arab.

P. crypsoides.—Plants collected in April 1962 from Burg El Arab, along the road from Cairo to Alexandria opposite kilo 166 from Cairo, and from Sidi Barrani.

P. coronopus.—Plants collected in April 1962 from Burg El Arab.

P. crassifolia.—Plants collected in June 1962 from the marshy areas along the highway from Alexandria to Burg El Arab oppposite kilo 23–27 from Alexandria.

P. major.—Plants collected in June 1962 from gardens, fields, and along canal banks in Giza.

P. cylindrica.—Plants collected in April 1962 from the eastern and western deserts.

P. albicans.—Plants collected in April 1962 from Burg El Arab, Dabaa, Ras El Hikma, and Sidi Barrani in the western Mediterranean coastal region.

P. ovata.—Plants collected in April 1962 from sandy areas of the gravel desert along Cairo-Suez road and from the Lybian desert along Cairo-Alexandria road.

The systematic identification of the plants was carried out by Dr. K. H. Batanouny, Faculty of Science, Cairo University.

Spikes of the plants were collected and dried in an air oven at 50°, and the mature seeds were obtained from the spikes by hand, difficult with *P. crypsoides*, *P. coronopus*, and *P. crassifolia*, due to the compactness and hardness of their fruits.

Mucilages

The seeds of plantago were reported by some authors (1–7) to be an excellent source of acid polysaccharides, the mucilages of which appeared to be mixtures of at least two polysaccharides differing in their uronic acid content (5, 6).

Preparation and Fractionation of the Mucilages.—Ten grams of plantago seeds were mixed with 1 L. of distilled water slightly acidified with hydrochloric acid (pH 3.5) at a temperature of about 20° and stirred for 12 hr. The highly viscous mucilaginous solution was passed through folded muslin. The process was repeated three times, and the mucilage was precipitated from the combined extract by adding, dropwise while stirring, 4 vol. of 96% ethanol. The precipitated mucilage, obtained by centrifugation, was washed several times with 96% ethanol until free from chloride ions, then vigorously stirred with absolute acetone, filtered, and dried in a vacuum desiccator.

The seeds after exhaustive extraction with cold water were washed with cold water till free from chloride ions and then extracted completely with hot water (90–95°). The mucilage was separated and purified in the same manner as with the cold fraction. The corresponding percentages of the different mucilage fractions are shown in Table I.

The hot fractions, though darker in color, gave the same tests of purity as the cold fractions. Both were starch-free, had no odor or taste, did not reduce Fehling solution, and gave negative tests for nitrogen. A paper chromatogram of the mucilage proved the absence of any sugar contaminant. All the mucilage fractions left slight residue on ignition (Table I).

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