THE ASSESSMENT OF ANTITUSSIVE DRUGS IN MAN

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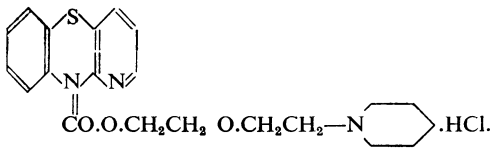
This paper describes a method which has been used to stimulate cough artificially in human subjects in order to assess the therapeutic activity of antitussive preparations. In the present work the method has been applied so as to compare the antitussive power of codeine phosphate, pipazethate hydrochloride ("selvigon"), and a placebo.

Pharmacology

Pipazethate is an ester of 1-azo-phenothiazine-10-carboxylic acid and has the following structure:



The pharmacology of pipazethate has been studied by Domenjoz (1960, private communication) and Gulden (1960). These authors report that pipazethate protects guinea-pigs and cats against cough produced by inhalation of sulphur dioxide or by electrical stimulation of the superior laryngeal nerve. Local anaesthetic potency, measured by the mousetail infiltration method, was about 40% of that of lignocaine; no analgesic activity could be demonstrated in mice even when the dose was increased to toxic levels.

Spasmolytic activity was studied on isolated guinea-pig gut. The potency of pipazethate in inhibiting barium-chloride-induced spasm was 1.6 times that of papaverine, but the drug was found to have only about 5% of the activity of atropine in inhibiting spasm induced by acetylcholine.

The 50% effective sleep-producing dose given orally in mice was 106 mg./kg.; thus therapeutic doses are not likely to produce sedation in man.

In mice the LD50 was 97 mg./kg. i.p. and 214 mg./kg. orally, and in rats the LD50 was 70 mg./kg. i.p. and 560 mg./kg. orally. The toxicity of the drug is thus low.

An effective antitussive dose by mouth in human subjects is 20 mg., which can be repeated up to at least 160 mg./day, though this level of dosage is seldom required in clinical situations. In therapeutic doses no side-effects have been noted. Dogs exposed to high daily dosage for six months showed no toxic reactions whatever.

Various methods have been tried in the past to provoke coughing in a controllable manner. Bickerman and Barach (1954) recommend the inhalation of solutions of citric acid from a nebulizer; they claim a very constant response to this form of stimulus in individual subjects which has not varied even after the lapse of years. Their method was to determine by trial and error the concentration of citric acid which it was necessary to administer in order to initiate coughing; concentrations of the order of 10% were required. Gravenstein, Devloo, and Beecher (1954) tried this method and several others, comparing the results with the effect of an inert substance, and concluded that none of them gave results which could be usefully applied to the human subject.

After considering these findings it was decided in the present instance to make use of an observation by Tiffeneau (1955, 1957) that the administration of a nebulized solution of acetylcholine chloride to certain subjects was regularly followed by more or less coughing. This method was applied to 12 healthy subjects all of whom were less than 30 years of age and were non-smokers. They inhaled a mist of the test solution for a period of one and a half minutes, but in no instance was coughing produced even with concentrations of acetylcholine of 1%. Other irritants were used, but all had disadvantages. Ether vapour, for example, at a concentration of the order of 3%, was tolerable, but the smell and taste of the vapour were objectionable to the subjects; low concentrations of sulphur dioxide were also tried, but the irritant was so powerful that none of the subjects wished to repeat the test. It was concluded that none of these procedures were useful for stimulating cough in entirely normal subjects, a conclusion which confirms Tiffeneau's findings.

The next step was to repeat the experiments on a different set of volunteer subjects. Twelve men were chosen who did not complain of symptoms of respiratory disease but who, on direct questioning, admitted that they habitually had a little cough. All of these, with the exception of two, were cigarette smokers consuming about 20 cigarettes a day. They ranged in age from 22 to 47 years and were in all other respects healthy so far as clinical and radiological examination could ascertain. When this group was subjected to the test procedure, all responded by coughing. Some started to cough before the end of the one and a half minutes of inhalation of 1% acetylcholine solution. It was found that the number of coughs produced in the 20 minutes after the test was fairly reproducible in a given subject on a given day, but the difference in the effect between different subjects was considerable. Presumably acetylcholine acts by stimulating the afferent vagal nerve-endings in the tracheo-bronchial mucosa, and the difference in susceptibility to the stimulus shown by different individuals is an expression of variations in irritability of these nerve-endings. These results encouraged us to carry out a planned experiment, having as its objective the comparison of the two cough-repressing drugs mentioned above.

Method

The experiment was carried out in the form of a double-blind trial using the 12 subjects mentioned above. Each subject breathed an aerosol of 1% acetylcholine chloride solution for one and a half minutes or until coughing began, and the number of coughs produced during the ensuing 20 minutes was counted. At the end of this time coughing had worn off. The subject then took a tablet of either pipazethate 20 mg. or codeine phosphate 16 mg. (¼ gr.), or an inert placebo tablet. After an interval of 20 minutes the test was repeated. To avoid any possibility of cumulative action of the test substances or any synergism between them only one substance was used in this way on any given day by each subject. The tablets were administered in random order on two occasions to each subject.

Results

The experimental design was such that there was an initial estimate of the cough rate in each subject after the test procedure and a similar estimate after administration of the tablets. Table I shows these cough rates. These results were subjected to an analysis of covariance (Fisher, 1944), which showed that there was a significant relation between the cough rates before and after taking the tablets; in other words, there is a real tendency, under the conditions of the experiments, for a subject whose initial cough rate is higher than the average before taking a tablet to have a rate higher than the average after taking it. This observation strengthens confidence in the technique of testing but must be allowed for in considering the mean cough rates after taking the tablets. With this allowance it can be shown that the mean cough rates after pipazethate, codeine, and placebo are respectively 4.6, 7.9, and 14.0. The difference between the cough rates after pipazethate and after codeine is significant, and between both these and that after the placebo is highly significant. There was no significant difference between the initial rates and those after the placebo. The steps in the analysis are presented in the Appendix to this paper.

TABLE I.—*Number of Coughs Produced During 20 Minutes of the Various Tests*

Subject	Age	Placebo		Codeine Phosphate		Pipazethate	
		A	B	A	B	A	B
1	22	7	9	9	6	6	0
2	27	10	12	9	6	11	5
3	23	12	9	11	8	10	3*
4	47	17	20	19	12	20	14
5	35	10	8	9	5	11	4
6	40	9	10	7	3	12	3
7	45	17	16	10	8	11	5
8	37	9	12	9	6	12	7
9	42	15	11	13	2	16	4
10	27	15	20	11	9	14	10
11	43	25	26	20	10	23	0*
12	28	19	21	18	9	20	6
Means	..	13·75	14·50	12·09	7·00	13·93	5·09

* Sulphur dioxide used instead of acetylcholine chloride.
A = Before taking the tablets. B = After administration of tablets.

Discussion

Two difficulties arise in designing a test for the effectiveness of an antitussive in man. The obvious test is to administer the drug to a patient with a disease that makes him cough. The objection to this is that the cough may improve by itself if the acute causal disease resolves. Moreover, it would be a matter of considerable difficulty to obtain the necessary control cough counts before giving the antitussive drug. The alternative is to devise some artificial method of inducing cough in normal subjects. It has already been pointed out that this was found to be impracticable.

Having found subjects in whom it is possible to induce cough, it is then necessary to calibrate the procedure in such a way that the effect of the drug may be measured. The best way to do this would be to measure the minimum stimulus required to produce cough. This is what Bickerman and Barach (1954) claim to have done; we were not so successful. Haslreiter (1959) also makes the same claim for the acetylcholine test which we have used, but here also we were not able to repeat this author's findings. The assumption which underlies the present work is that the response to the test, in terms of cough rate, is a measure of the strength of the stimulus. It may be said in favour of this method that it resembles more closely the situation met with in clinical work in which the strength of the stimulus is not necessarily minimal and may be very strong. If patients serve as their own controls it is possible to use the technique to obtain a meaningful answer.

These experiments show that pipazethate is a potent antitussive drug. When any preparation as active as this is introduced it becomes necessary to have as clear an idea as possible of the indications for its use as well as of the correct dosage. In general, antitussives should be given only to those patients in whom the cause of coughing is known with certainty and in whom this symptom urgently needs to be controlled. Thus when an unproductive cough associated, for example, with heart disease or chronic pulmonary disease is hindering sleep or exhausting an enfeebled patient, it is justifiable to administer such a drug as this or codeine. On the other hand, a cough productive of large quantities of infected sputum should never be treated in this way for fear of encouraging sputum retention, with the concomitant danger of aspiration pneumonia. It has been found possible to suppress cough in chronic bronchitics completely by giving the drug in a dose of 160 mg. by mouth. No side-effects were observed, apart from the abolition of cough, and this suggests that the absence of side-effects may make it easier to give an overdose of pipazethate than of a drug such as codeine.

The dosage which has been found adequate for most purposes is 20–40 mg. in a single dose by mouth and up to about 160 mg. in 24 hours. In this dose range no side-effects have ever been observed with this drug in my, at present rather limited, experience, nor has coughing been depressed to such a level that the patients were not aware that they ought to cough up some sputum. One of the desirable features in the action of pipazethate is that coughing, when it does occur, is diminished in violence and is therefore less exhausting than it otherwise might be. Another important field of use for pipazethate is in the premedication of patients who are to be submitted to peroral endoscopy or bronchospirometry where the stimulus to coughing is about as severe as it can possibly be. The administration of a small dose of pipazethate (10 mg.) intravenously about 10 minutes before the procedure makes it much easier and reduces the amount of topical anaesthetic required (Gregoire, Thibaudeau, and Comeau, 1958).

Summary

A method of inducing cough described by Tiffeneau has been successfully used for comparing the antitussive potency of codeine and pipazethate hydrochloride. This shows that both drugs are about equally effective; the latter has the advantages that it produces no undesirable side-effects and is useful for facilitating procedures involving peroral endoscopy.

My thanks are due to those patients and friends who voluntarily submitted to the tests; their comments were often helpful. I am grateful to Messrs. Smith Kline and French, who gave me supplies of selvigon and who defrayed the expenses of the investigation.

APPENDIX

The results given in Table I were examined by standard covariance analysis using x, the cough rate in the control period, as the covariance variate, and y, the cough rate after taking the tablets, as the dependent variate. Table II shows the analysis.

The estimate, S^2, of the error variance is 200.5/21, or 9.55. Testing the mean square for regression against

this value of S^2, we obtain a variance ratio of 4.859, which for 1 and 21 D.F. is statistically significant ($0.025<P<0.05$). It is thus necessary to correct the mean cough rates after the three drugs for differences in the initial cough rates.

The corrected sum of squares for drugs was obtained by Fisher's exact method (Fisher, 1944, p. 275). The procedure gives a corrected sum of squares of 552.9 with 2 D.F.; the mean square is thus 276.45, giving a variance ratio of 28.948, which is highly significant ($P<0.001$). Since a significant difference between the three types of tablet is thus demonstrated, we proceed to test the individual differences pipazethate *v.* codeine, pipazethate *v.* placebo, and codeine *v.* placebo, correcting the mean cough rate after each drug ($\bar{y}$) for differences in the corresponding mean initial cough rates ($\bar{x}$). The corrected mean is given by the expression

$$\bar{y}_c = \bar{y} - b(\bar{x} - \bar{\bar{x}})$$

where b is the coefficient of regression of y on x and $\bar{\bar{x}}$ is the grand mean initial cough rate; in the present instance the values of b and $\bar{\bar{x}}$ are 0.83 and 13.2 respectively. Table III shows the values of $\bar{x}$, $\bar{y}$, and $\bar{y}_c$ for the three drugs.

TABLE II

Source of Variation	Degrees of Freedom	Sum of Squares and Products		
		x^2	xy	y^2
Total	35	812·2	496·1	1,242·3
Subjects	11	721·5	406·8	401·0
Drugs	2	23·4	33·4	574·4
Subjects × drugs	22	67·3	55·9	246·9
Regression	1	—	—	46·4
Remainder	21	—	—	200·5

TABLE III

	Pipazethate	Codeine	Placebo
$\bar{x}$	13·8	12·1	13·8
$\bar{y}$	5·1	7·0	14·5
$\bar{y}_c$	4·6	7·9	14·0

The variance of an adjusted mean of n observations is given (Finney, 1952, p. 51) by the expression:

$$V(\bar{y}_c) = S^2\left(1/n + \frac{(\bar{x}-\bar{\bar{x}})^2}{S_{xx}}\right)$$

where S_{xx} is the error sum of squares for the covariance variate. Strictly speaking, a separate variance should be calculated for each mean; in the present instance, however, since all three means are based on the same number of observations (12) and the differences between the three values of $(\bar{x}-\bar{\bar{x}})$ are small compared with S_{xx}, it is permissible to use a single estimate of the error variance based on the largest value of $(\bar{x}-\bar{\bar{x}})$. This procedure slightly underestimates the significance of the differences between the means. The estimate of V ($\bar{y}_c$) thus obtained is 9.55 $\left(1/12 + \frac{(1.1)^2}{67.3}, \text{ or } 0.9646\right)$, giving the estimated standard error of any mean as 0.9821. Using this estimate of the standard error, the differences between the three adjusted means were tested by Duncan's (1955) multiple-range test. This procedure shows that the difference between pipazethate and codeine is significant at the 5% level, and the differences between pipazethate and placebo and between codeine and placebo are significant at the 1% level.

We may therefore conclude that both pipazethate and codeine produce real protection against the cough-producing effects of an acetylcholine aerosol, and that pipazethate is significantly more effective than codeine.

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Medical Memoranda

Temporal Arteritis Resulting in Infected Gangrene of Tongue

The tongue has an excellent multiple blood supply. Occlusion of any one artery is therefore unlikely to result in ischaemic atrophy or gangrene. These conditions may be produced only by a generalized arterial lesion or possibly by a massive infection. In the following case such a state was produced by temporal arteritis, which presumably resulted in widespread occlusion of the arterial supply to the tongue.

CASE HISTORY

A woman of 82 was admitted to hospital on August 25, 1959, as a medical emergency, suffering from a swollen tongue. No history was available on admission, but later the following facts became known. She had had herpes zoster of the right loin two years previously. One month prior to admission she felt generally unwell with no specific complaints. She then developed red raised areas over the forehead and the right side of the scalp, associated with localized headaches of moderate severity. She was treated by her own practitioner as a developing case of herpes zoster, with vitamin B_{12} twice weekly for three weeks. Her general condition remained stationary until 24 hours before admission, when she suddenly developed severe and intractable pain in the right side of her head only partially relieved by pethidine. This was followed in eight hours by a sudden increase in the size of her tongue, which seemed to fill her mouth and made articulation impossible.

On examination her general condition was poor. She was inarticulate and unable to close her mouth. She had considerable respiratory embarrassment from obstruction to her airway except when bending forward. The skin of her face showed a general cyanotic tinge with a reddened, slightly raised area in the right temporo-parietal region. The tongue appeared enlarged, was heavily furred, and was lacking in tone or voluntary movement. The general appearance was that this organ had been deprived of its blood supply. Her pulse was regular and blood-pressure 180/90; bilateral carotid pulses were present; temporal arteries were not palpable.

To obviate respiratory obstruction by the tongue falling back into the pharynx when lying down, a silk suture was passed through the tongue ½ in. (1.3 cm.) from the tip in the midline and fastened forward by securing the free end of the suture to the cheek with plaster. This manœuvre appeared to be painless and produced no bleeding whatsoever. Tube feeding and oral toilet were carried out frequently, and the following progress was noted.