RESEARCH PAPERS

ANTITUSSIVE AND OTHER PHARMACOLOGICAL PROPERTIES OF THE DIETHYLAMINOETHOXYETHYL ESTER OF αα-DIETHYLPHENYLACETIC ACID, (OXELADIN)

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The diethylaminoethoxyethyl ester of αα-diethylphenylacetic acid (oxeladin) appears to possess similar antitussive activity to carbetapentane and to be slightly less active than codeine phosphate. Sensory nerve endings in the trachea and bronchial tree are not the site of action. The acute toxicity is not significantly different from that of carbetapentane. The ester is two to four times as toxic as codeine phosphate, according to species and route of administration. It has local anaesthetic properties, being approximately twice as active as procaine hydrochloride by the guinea pig intracutaneous wheal test. Only excessive amounts appear to have a constipating effect in normal mice. A spasmolytic effect has been demonstrated with the isolated guinea pig ileum and isolated rabbit duodenum. It has, however, a spasmogenic effect on the jejunum of the anaesthetised cat. Intravenous injection in the anaesthetised cat produced a transient fall in blood pressure of the same magnitude as that produced by codeine phosphate. It has been administered to rats over a prolonged period with no untoward effect on the growth rate and the haemopoietic system.

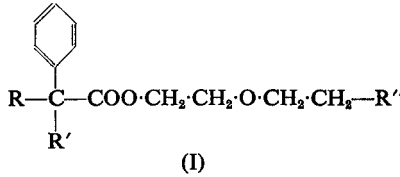
THE cough reflex serves a useful purpose in removing irritants from the larger bronchi and upper air passages. Frequently, however, coughing is due to hyper-excitability of the throat and bronchi and this results in a dry, unproductive cough causing considerable distress. A useless cough of this nature is usually treated with one of the opium alkaloids or their derivatives which have a depressant action on the cough centre in the medulla. They have the disadvantages that in addition to a liability to cause addiction, they have a respiratory depressant action, produce drowsiness and cause constipation.

The search for a non-opiate type of antitussive is hindered by the lack of a completely satisfactory method for testing new compounds, as evidenced by the multiplicity of methods used in recent years. These have differed in the means used to elicit coughing, in the species employed and according to whether the animal was conscious or anaesthetised. Winter and Flataker[1] induced coughing in conscious dogs by means of an aerosol of sulphuric acid, and in a later paper[2] they described the exposure of conscious dogs and guinea pigs to an aerosol of ammonia solution. The direct introduction of sulphur dioxide into the trachea of the anaesthetised cat by May and Widdicombe[3] and Green and Ward[4] and the guinea pig[4] has also been employed. Mechanical stimulation of the trachea has been carried out in the anaesthetised cat[3,4] and also in the

anaesthetised dog and guinea pig[4]. Finally, various forms of electrical stimulation have also been used; Stefko and Benson[5] used electrodes embedded in the trachea of conscious dogs and Chakravarty, Matallana, Jensen and Borison[6] produced coughing by electrical stimulation of the medulla of the decerebrate cat. The most widely used method, has been that of Domenjoz[7] (see refs. 4, 8, 9), involving electrical stimulation of the superior laryngeal nerve of the anaesthetised cat.

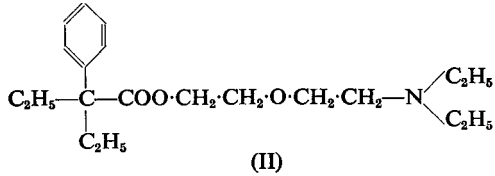
We used this latter method in our investigations for a number of reasons. It is easy and two compounds can be compared at several dose levels in the same animal, the cough being reproducible over a prolonged period. In addition, Green and Ward[4] found that the experimental cough produced by stimulation of the superior laryngeal nerve responded to various drugs in the same way as cough caused by mechanical and chemical irritation of the bronchial system. They concluded that the same afferent fibres are probably involved. They also compared the results of others with their own and found that, in general, the activities of recognised antitussives did not vary to any great extent either with the stimulus used for initiating the reflex or with the species and that results obtained in lightly anaesthetised animals are similar to those in conscious animals. The method is also of value since stimulation of the central cut end of the superior laryngeal nerve excludes any compound having a purely local action on the sensory nerve endings in the respiratory tract.

Twelve compounds, prepared by Dr. V. Petrow and his colleagues of the B.D.H. Chemical Research Department, have been examined for antitussive activity. These may be considered to be derived from the ethoxyethyl ester of phenylacetic acid and have the general formula I.



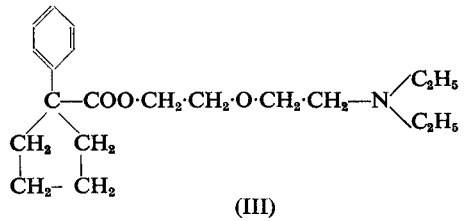
(I)

The diethylaminoethoxyethyl ester of αα-diethylphenylacetic acid (II, oxeladin, appeared the most promising in preliminary studies and was selected for further investigation. A related compound, the diethylaminoethoxyethyl ester of 1-phenyl-1-*cyclo*pentane carboxylic acid (III, carbetapentane), also possesses antitussive properties[9] and was used as a reference compound.



(II)

Oxeladin



(III)

Carbetapentane

Comparisons with codeine phosphate were also made.

Oxeladin has a molecular weight of 335. The free base is a yellow, slightly viscous fluid with an acrid odour and a bitter, aromatic flavour. It is soluble in dilute hydrochloric acid, ethanol and acetone but is insoluble in water. It is stable in acids but is unstable in alkalis. It is non-hygroscopic and is stable up to 150°.

METHODS

Antitussive Activity

Male and female cats weighing 2·8 to 4·4 kg. were anaesthetised with 5 per cent sodium pentobarbitone, 25 to 90 mg./kg., injected intraperitoneally. The anaesthetic was administered in divided doses until an adequate yet light anaesthesia was obtained. The right or left superior laryngeal nerve was identified by means of its sinuosity ventral to the carotid artery at the level of the larynx. The nerve was dissected and, in the earlier experiments, placed intact over platinum electrodes of the open-jaw type. In later experiments, the nerve was cut close to the larynx and the central end laid across the electrodes. This avoided muscle twitches around the larynx due to stimulation of efferent nerve fibres. More recently, platinum electrodes described by Bülbring[10] for the rat phrenic nerve-diaphragm preparation were used to stimulate the cut end of the nerve which was kept moist with normal saline. These electrodes gave better contact. The trachea was cannulated in the majority of experiments and although the larynx, vocal cords and glottis could not participate in the cough response, auditory recognition of a cough was possible. Diaphragmatic movements were recorded on smoked paper by an isometric lever attached by a thread to the abdominal wall just caudal to the xiphisternum. The animal was then left undisturbed for at least forty-five minutes to lighten the degree of anaesthesia. Thereupon, the nerve was stimulated for periods of five seconds with an electronic stimulator (Newton Victor Ltd.), the pulses being of 10 m. sec. duration and at a frequency of five per second. The stimulus intensity required to elicit a reproducible cough was determined and was found to be within the range 0·5 to 4 volts. Stimuli of this intensity were applied for five seconds at five minute intervals throughout the remainder of the experiment. The compounds were injected via the cannulated femoral vein at times halfway between two successive stimuli. At least three successive satisfactory cough responses were obtained before any dose

was injected. The effects of two compounds were usually compared at several dose levels in each animal, the doses being injected in a random order. Oxeladin and carbetapentane were injected in 5 per cent acacia and codeine phosphate in aqueous solution.

Acute Toxicity

Intravenous toxicity was estimated in male albino mice weighing approximately 20 g. Oxeladin and carbetapentane were emulsified in 5 per cent acacia and codeine phosphate was dissolved in distilled water. The volume administered was adjusted to 0·2 ml./20 g. weight. Each compound was examined at three or four dose levels which increased in geometrical progression by a factor of 4/3. Oral toxicity was estimated in male albino mice weighing approximately 20 g. and in female albino rats weighing approximately 120 g. The animals were starved overnight before use. The volume administered was adjusted to 0·5 ml./20 g. weight for both mice and rats. Each compound was examined at four or five dose levels increasing by a factor of 7/5 for mice and 4/3 for rats. Ten animals were used at each dose level in all experiments. LD50s were calculated by the method of Litchfield and Wilcoxon[11] from the mortalities in seven days.

Subacute Oral Toxicity

This was investigated in immature male albino rats. The compounds were administered by stomach tube five days a week for eleven weeks. Each compound was given at three dose levels (7, 20 and 60 mg./kg. weight/day) such that the daily dose corresponded to approximately 5, 15 and 45 per cent of the acute oral LD50 in mice. The animals were weighed at weekly intervals and the doses were related to the individual body weight at the beginning of each week. All volumes were adjusted to 25 ml./kg. weight. Ten animals were used at each dose level and a further group of ten animals served as controls; these were given only the vehicle, 5 per cent acacia. The animals were kept under identical conditions and were allowed Diet 41 and water *ad lib.* At the end of the experimental period haemoglobin estimations, total red and white cell counts and differential white cell counts were made on the control animals and the survivors on the high dose of each compound. Histological examination of liver, spleen, kidney, lung and stomach from three animals in these groups was also made.

Local Anaesthetic Activity

This was measured in shaved guinea pigs using the intracutaneous wheal method of Bülbring and Wajda[12]. The animals were divided into three groups of eight given either high, medium or low concentrations of the compounds. Four animals from each group were injected with the citrate salt of oxeladin in the anterior part and with procaine hydrochloride in the posterior part of the shaved area. The positions of the compounds were reversed in the remaining animals of the group. The order of injections was unknown to the observer. Each dose was injected

intracutaneously in the mid line in 0·2 ml. of normal saline. The resultant wheal was outlined in ink and the response to six pin pricks within this area was determined five minutes after injection and then at five minute intervals for thirty minutes. The number of negative responses to the total of 36 stimuli was recorded. The mean of the eight results for each concentration was estimated and plotted against the log of the concentration.

Action on the Gastrointestinal Tract

Isolated rabbit duodenum. Segments of rabbit duodenum were suspended in Ringer-Locke solution in a 70 ml. bath maintained at a temperature of 37°. A mixture of oxygen and 5 per cent carbon dioxide was bubbled through the solution. Normal rhythmic contractions were obtained and varying volumes of 0·1 and 1·0 per cent solutions of the water-soluble citrate salt of oxeladin were added at intervals. The compound was allowed to act for two minutes before washing out.

Isolated guinea pig ileum. Spasmolytic activity was estimated using the isolated guinea pig ileum. A 4 cm. segment was suspended in Ringer-Locke solution in a 25 ml. bath maintained at 37°. A mixture of oxygen and 5 per cent carbon dioxide was bubbled through the solution. Sub-maximal doses of acetylcholine (0·3 μg.) were added at three minute intervals and allowed to act for thirty seconds before washing out. Varying amounts of methantheline bromide and the citrate salt of oxeladin were added thirty seconds before the addition of acetylcholine. At least three normal responses to acetylcholine were obtained between doses of the spasmolytics. The heights of the contractions immediately before and after the addition of the spasmolytic were measured. The inhibition per cent was plotted against log dose and the amount causing 50 per cent inhibition calculated.

Spasmolytic activity was also estimated against a barium chloride spasm. The guinea pig ileum was suspended in oxygenated Tyrode solution and sub-maximal doses of barium chloride (2·0 mg.) were allowed to act for 45 seconds at three minute intervals. Varying amounts of papaverine hydrochloride and the citrate salt of oxeladin were added one minute before the addition of barium chloride.

Defaecation. The method was based on that described by Lou[13] for the assay of vegetable purgatives. Male albino mice weighing approximately 20 g. were divided into four groups of nine animals. Three groups were given varying amounts of oxeladin corresponding to approximately 5, 15 and 45 per cent of the acute oral LD50 in mice. The compound was administered orally as its citrate salt in aqueous solution, the volume being adjusted to 0·5 ml./20 g. weight. The fourth group served as controls, being given a similar volume of water. Fifteen minutes after administration, the mice were placed in individual compartments over a wire grid and the faeces collected on blotting paper. The fifteen minutes interval was considered advisable as defaecation frequently occurred after the initial handling. The mice were given a paste of diet 41 and water throughout the experiment. The total number

of faecal pellets from each animal was counted at 8 and 24 hours after administration.

Cat Jejunum in situ. The cat was anaesthetised with ether followed by chloralose, 60 mg./kg. intravenously. A water-filled balloon was inserted into the jejunum through an abdominal incision and contractions were recorded by means of a water and air transmission system connected to a small piston recorder. The pressure in the balloon was approximately 10 cm. of water. When spontaneous rhythmic contractions were established, the citrate salt of oxeladin was injected into the cannulated femoral vein.

Effect on Blood Pressure and Respiration of the Anaesthetised Cat

Male and female cats weighing approximately 3 kg. were anaesthetised with ether followed by chloralose, 60–80 mg./kg., intravenously. The carotid arterial blood pressure was recorded by means of a mercury manometer, and 500 units of heparin were injected intravenously to prevent clotting. Respiration was recorded by means of a float recorder connected via uni-directional valves[14] to a tracheal cannula. The compounds were injected into the cannulated femoral vein.

RESULTS

Antitussive Activity

The usual cough response after electrical stimulation of the superior laryngeal nerve consisted of a series of inspiratory gasps culminating in one or more explosive expirations. The sound produced by the violent expiratory component could be readily recognised and was similar to a normal cough, even in those animals with a cannulated trachea. The cough was recorded as a considerable excursion of the isometric lever following movements of smaller magnitude during the inspiratory gasps. The effect of an antitussive compound was, in completely effective doses, to abolish both the inspiratory gasps and the violent expiratory components. The cough sound was consequently absent and there were no movements of the isometric lever. After smaller doses, or sometimes during recovery from a large dose, the violent expiratory component was again abolished but the series of inspiratory gasps was unaltered or

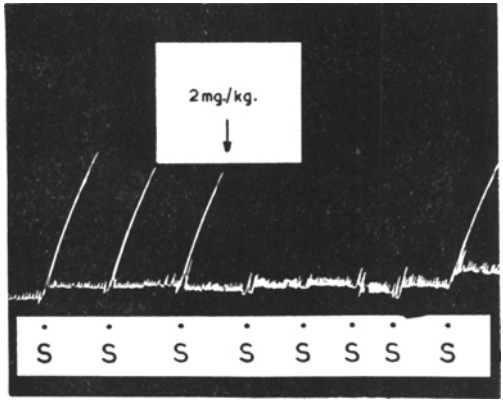


FIG. 1. Effect of intravenous injection of oxeladin at arrow in a 2·9 kg. cat anaesthetised with sodium pentobarbitone, 65 mg./kg. intraperitoneally. Movements of the xiphisternum after electrical stimulation (at S) of the superior laryngeal nerve for 5 seconds at 5 minute intervals.

slightly moderated. The excursions of the isometric lever were therefore markedly reduced but not abolished, whilst the cough sound was absent. Figure 1 shows a typical result, there being no response to the first two stimuli after injection of oxeladin, whilst the third and fourth stimuli resulted in a few inspiratory gasps.

Although oxeladin was compared directly with either codeine phosphate or carbetapentane in each animal, the results are difficult to evaluate because of the variability of the effects within the individual animal. This may be attributed to a changing level of anaesthesia throughout the experiment and possibly to residual effects from previous doses. The kymograph records of each experiment were carefully examined and the effects of each dose evaluated according to two criteria.

TABLE I

APPROXIMATELY EQUI-EFFECTIVE DOSES OF OXELADIN, CODEINE PHOSPHATE AND CARBETAPENTANE AGAINST THE COUGH PRODUCED BY ELECTRICAL STIMULATION OF THE SUPERIOR LARYNGEAL NERVE IN ANAESTHETISED CATS

Experiment	Compound		
	Oxeladin mg./kg.	Codeine phosphate mg./kg.	Carbetapentane mg./kg.
1	2	2	
2	2	1	
3	4	1·5	
4	1	2	
5	2	2	
6	4		4
7	4		2
8	6		8
9		1·5	3
		3	6
10		4	4
11		2	4

These were, intensity of effect, according to whether there was complete suppression of the cough reflex or whether only the expiratory component was prevented; and the duration of effect. The amount of each compound producing approximately the same intensity of effect for approximately the same duration was then noted. The results of this analysis are shown in Table I. It appears that the relative activity of two compounds varies widely in different animals, and this confirms the observation of Toner and Macko[8] who used a similar experimental procedure. They found that in some animals one compound was active whilst another was inactive but that the converse was true in other animals. It is not possible, therefore, to arrive at a strictly quantitative assessment of the relative activities of the three compounds examined. Inspection of the results in Table I indicates that oxeladin and carbetapentane are probably equally active, and that codeine phosphate may be slightly more active.

All three compounds were effective against stimulation of the central cut end of the nerve as well as against stimulation of the intact nerve. The site of action, therefore, would not appear to be on sensory nerve endings in the upper respiratory tract.

Acute Toxicity

The results are recorded in Table II. Similar estimates of LD50 were obtained for oxeladin and carbetapentane in all experiments. They are two to three times as toxic as codeine phosphate after oral administration in mice and rats and are about four times as toxic as codeine phosphate intravenously in mice. Lethal doses of oxeladin and carbetapentane caused the mice to convulse within a few minutes. The convulsions were interrupted by short periods of quiescence during which the

TABLE II

THE ACUTE TOXICITY OF OXELADIN, CODEINE PHOSPHATE AND CARBETAPENTANE. THE MEDIAN LETHAL DOSE ESTIMATED BY THE GRAPHICAL METHOD OF LITCHFIELD AND WILCOXON[11]

Compound	Species	Route of administration	LD50 mg./kg.	Limits of error (P = 0·95), mg./kg.
Oxeladin	Mouse	Intravenous	13	12–15
Codeine phosphate ..			53	43–65
Carbetapentane ..			13	11–15
Oxeladin	Mouse	Oral	130	108–156
Codeine phosphate ..			300	252–357
Carbetapentane ..			130	108–156
Oxeladin	Rat	Oral	183	136–247
Codeine phosphate ..			420	341–517
Carbetapentane ..			150	117–192

TABLE III

THE EFFECT OF CONTINUED ORAL ADMINISTRATION OF OXELADIN AND CARBETAPENTANE ON THE MEAN WEIGHTS OF GROUPS OF TEN MALE ALBINO RATS

Compound	Dose/day mg./kg.	Time in weeks 0	1	2	3	4	5	6	7	8	9	10	11
—	—	97	116	132	155	174	195	200	214	226	234	236	243
Oxeladin	7	97	113	132	152	174	187	191	201	213	220	226	234
	20	96	112	134	*156	172	196	208	219	230	235	240	248
	60	96	*113	140	151	171	198	207	219	229	238	241	244
Carbetapentane	7	95	113	133	151	164	183	191	198	213	218	228	234
	20	97	111	132	*150	155	189	198	207	*212	205	212	221
	60	96	111	*119	138	162	184	196	206	210	222	226	232

* One animal died during the preceding seven days.

righting reflex was absent. Gasping respiration, which persisted for several minutes, preceded death. A few minutes after lethal doses of codeine phosphate, the mice showed increased activity with the tail generally held erect. This was followed by convulsions which terminated suddenly in death.

Sub-acute Oral Toxicity

Table III shows the effect of varying doses of oxeladin and carbetapentane on the mean weights of rats during a period of eleven weeks. After four weeks the group given 7 mg./kg./day of oxeladin gained weight somewhat more slowly than did the control group. This does not appear to be due to cumulative toxicity, however, as the animals given 20 and 60 mg./kg./day gained weight at the same rate as the

control group. All three groups given carbetapentane gained weight at somewhat slower rates than the controls. A limited number of deaths occurred during the treatment period as indicated in the Table, but these may have been due to an intercurrent infection. Histological examination of liver, spleen, kidney, lung and stomach from animals given the high

TABLE IV

THE EFFECT OF CONTINUED ORAL ADMINISTRATION OF OXELADIN AND CARBETAPENTANE (60 MG./KG. FIVE DAYS A WEEK FOR ELEVEN WEEKS), ON THE MEAN HAEMATOLOGICAL VALUES OF MALE ALBINO RATS

Compounds	No. of rats	Haemoglobin per cent	Erythrocyte count cells/cu. mm.	Leucocyte count cells/cu. mm.	Lymphocytes per cent	Polymorphs per cent	Monocytes per cent	Eosinophils per cent
—	10	109	7,270,000	17,000	83	14	<2	1
Oxeladin	9	110	7,440,000	17,600	82	17	<1	<2
Carbetapentane	8	110	7,270,000	17,000	84	14	<1	<1

doses of oxeladin and carbetapentane revealed no abnormalities compared with the control group. There were also no significant differences in the haematological values of the animals in these three groups at the end of the treatment period. The mean values are recorded in Table IV.

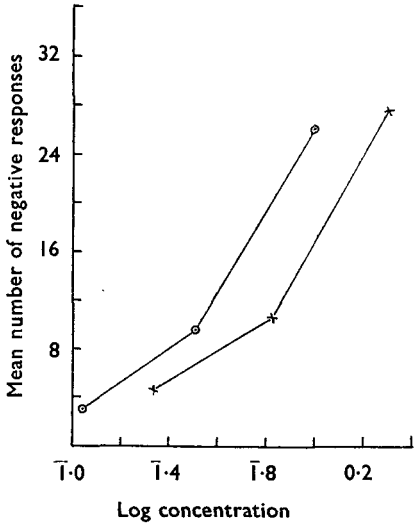


FIG. 2. Local anaesthetic activity of oxeladin (⊙——⊙) and procaine hydrochloride (×——×). Guinea pig intracutaneous wheal test.

Local Anaesthetic Activity

Figure 2 shows the mean number of stimuli giving negative responses plotted against log concentration of oxeladin and procaine hydrochloride. The dose-response line does not appear to be linear over the complete range of concentrations examined, but the two curves are parallel. Thus the relative activities of the compounds can be determined from the concentrations producing 50 per cent anaesthesia. The value for oxeladin was 0·58 per cent and for procaine hydrochloride 1·10 per cent; oxeladin appears to be about twice as active an infiltration local anaesthetic as procaine hydrochloride. It also appears to be absorbed from the conjunctiva as a 1 per cent solution produced local anaesthesia in the rabbit's eye. This was not fully investigated. There was no evidence that the varying concentrations of oxeladin produced local irritation or tissue damage.

Action on the Gastrointestinal Tract

Isolated rabbit duodenum. Oxeladin had little or no effect on the normal rhythmic contractions of three preparations in amounts below 0·1 mg. Amounts from 0·1 to 0·8 mg. produced varying degrees of reduction in tone associated with some reduction in amplitude of contractions. Larger amounts produced considerable loss of tone and

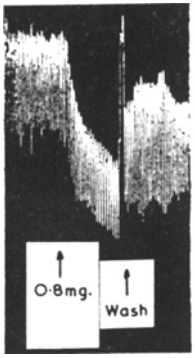


FIG. 3. Effect of oxeladin at arrow (0·8 mg. in 70 ml. bath for 2 minutes) on pendular movements of isolated rabbit duodenum.

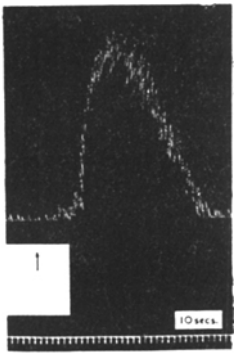


FIG. 4. Effect of intravenous injection of oxeladin at arrow on intact jejunum of 2·7 kg. cat anaesthetised with chloralose, 60 mg./kg. intravenously.

almost total inhibition of contractions. Spontaneous rhythmic contractions were readily resumed on washing-out after amounts up to 0·8 mg., but after larger amounts two or three wash-outs were required. Figure 3 records a typical response.

TABLE V

THE EFFECT OF OXELADIN AND METHANTHELINE BROMIDE ON ACETYLCHOLINE-INDUCED CONTRACTIONS OF ISOLATED GUINEA PIG ILEUM

Compound	Dose μg.	Reduction per cent	Dose causing 50 per cent reduction, μg.
Oxeladin	10 20 40	22 57 91	17·5
Methantheline bromide	0·02 0·04 0·08	27 65 97	0·03

Isolated guinea pig ileum. The spasmolytic activity of oxeladin is recorded in Tables V and VI. It appears that oxeladin has approximately 1/600 of the activity of methantheline bromide against acetylcholine induced contractions and approximately 2·5 times the activity of papaverine hydrochloride against barium chloride.

Defaecation. There was a 50 per cent reduction in the number of faecal pellets passed in eight hours after 200 mg./kg. of oxeladin compared

with the controls. During the following sixteen hours, however, there was no significant reduction in the number of faecal pellets. Oxeladin had no effect at lower doses. The results are recorded in Table VII.

TABLE VI

THE EFFECT OF OXELADIN AND PAPAVERINE HYDROCHLORIDE ON BARIUM CHLORIDE INDUCED CONTRACTIONS OF ISOLATED GUINEA PIG ILEUM

Compound	Dose µg.	Reduction per cent	Dose causing 50 per cent reduction, µg.
Oxeladin	10 20 40 80	22 31 65 99	28
Papaverine hydrochloride	50 100 200	34 64 93	74

Cat jejunum in situ. In a cat weighing 2·7 kg. anaesthetised with chloralose, 0·5 and 1·0 mg./kg. of oxeladin produced a considerable increase in the tone of the jejunum. The increase was gradual and commenced after a latent period of about one minute. Maximum tone was maintained for a brief period and was followed by a gradual return to the initial level. Figure 4 illustrates a typical result. 0·25 mg./kg. had no effect.

TABLE VII

THE EFFECT OF OXELADIN ON THE NUMBER OF FAECAL PELLETS PASSED BY MALE ALBINO MICE DURING TWO PERIODS AFTER ORAL ADMINISTRATION

Dose mg./kg.	Mean number of faecal pellets per animal	
	0–8 hours	8–24 hours
0	23	76
20	20	85
70	18	76
200	12	71

Effect on Blood Pressure and Respiration of the Anaesthetised Cat

The effect of oxeladin was examined in three cats weighing 2·7 to 3·0 kg. Amounts corresponding to 1·0 and 2·0 mg./kg. caused a rapid fall in blood pressure with recovery within a few minutes, whilst smaller amounts had little or no effect. Equal amounts of codeine phosphate produced effects of similar magnitude. The fall in blood pressure was not abolished by section of both vagi. Oxeladin, 2 mg./kg., caused a slight increase in respiratory minute volume. Figure 5 compares the effects of oxeladin and codeine phosphate in the same animal.

DISCUSSION

It appears that oxeladin is a potent antitussive in the anaesthetised cat. In general, the pharmacological properties which we have examined are similar, both qualitatively and quantitatively, to those of carbetapentane which it resembles structurally. Both compounds are two to four times as toxic as codeine phosphate, according to species and route of administration, and both appear to be only slightly less active than codeine phosphate in suppressing experimental cough in the anaesthetised

cat. Levis, Preat and Moyersoons[9] claimed that carbetapentane is 1·5 times as active as codeine phosphate as an antitussive, but our results have not confirmed this, possibly due to differences in the criteria used for interpreting the results. Oxeladin and carbetapentane also have similar local anaesthetic activity, being two and three times as active, respectively, as procaine by the intracutaneous wheal test in guinea pigs. Finally, the two compounds have similar spasmolytic properties, being weakly active against acetylcholine-induced contractions of the guinea pig ileum and about three times as active as papaverine against barium chloride-induced spasm.

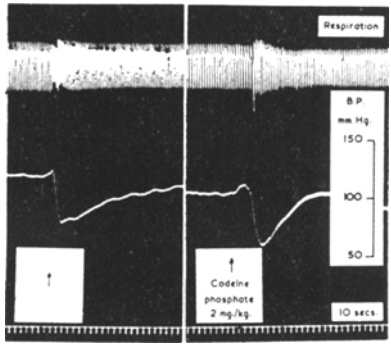


FIG. 5. Effects of intravenous injection of oxeladin at arrow and codeine phosphate on blood pressure and respiration of 3·0 kg. cat anaesthetised with chloralose, 80 mg./kg. intravenously.

As a result of their investigations on a series of compounds, Levis, Preat and Moyersoons[9] concluded that carbetapentane possessed greater antitussive activity than the *cyclo*propane, *cyclo*butane and *cyclo*hexane analogues. It appears from our experiments, however, that the *cyclo*pentane ring is not essential for maximal antitussive activity. Oxeladin differs from carbetapentane in that it is derived from αα-diethylphenylacetic acid instead of from 1-phenyl-1-*cyclo*propane carboxylic acid. Our results indicate that there is no marked alteration in activity consequent upon opening the *cyclo*propane ring.

The daily oral administration of oxeladin for eleven weeks did not appear to produce any untoward effects in immature rats, and no irritant effects have been observed after administration by oral and intracutaneous routes. A weak spasmolytic action was observed with isolated guinea pig ileum and rabbit duodenum preparations but, in contrast, oxeladin had a spasmogenic action on the jejunum of the anaesthetised cat. Only large amounts appeared to cause constipation in normal mice. In view of its efficacy in the suppression of experimentally-induced cough and the absence of undesirable pharmacological effects at therapeutic dose levels, oxeladin has been submitted for clinical trial.

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