SOME ASPECTS OF THE PHARMACOLOGY OF DROPERIDOL

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SUMMARY

The effects of droperidol, its solvent, and fentanyl on analgesia and respiration were examined in mice. Neither droperidol nor its solvent had analgesic properties, but droperidol was capable of potentiating both the analgesic and respiratory depressant effects of fentanyl. The peripheral actions of droperidol were examined on the guinea-pig ileum preparation. Antagonism of acetylcholine and histamine was demonstrated and shown to be non-competitive in nature. Local anaesthetic activity was detectable in the guinea-pig and the implications of these findings are discussed.

Droperidol is used both as a premedication and, in combination with fentanyl, for the maintenance of neuroleptanalgesia. There are some inconsistencies in the literature about certain aspects of the pharmacological activity of droperidol.

First, in the clinical situation droperidol has been reported to potentiate the analgesic activity of fentanyl (Foldes et al., 1964). However, using the technique of tibial pressure algesimetry in man Morrison (1970) reported antagonism of the analgesic activity of fentanyl.

Secondly, there is controversy over the mechanism by which droperidol produces its vascular effects. Droperidol lowers blood pressure in both the experimental animal (Yelnosky, Katz, and Dietrich, 1964) and in man (Macdonald et al., 1966). Corssen, Domino and Sweet (1964) ascribed this action to α-blocking activity. This explanation has been questioned by Whitwam and Russell (1971) and by Puddy (1971). The latter found, in vitro, that similar concentrations of droperidol antagonized the vasoconstrictor effects of histamine and potassium ion as well as noradrenaline.

The following experiments were designed to investigate the activity of droperidol as an analgesic, alone and in combination with fentanyl and to investigate the mechanism by which droperidol antagonizes spasmogens, in vitro.

Droperidol solvent contains lactic acid, methyl-p-hydroxybenzoate and propyl-p-hydroxybenzoate. It has been suggested that the preservatives in the solvent may possess local anaesthetic activity (Whitwam and Russell, 1971). Puddy (1971) pointed out that, in his own work, he had not eliminated the possibility that droperidol solvent was responsible for some of the actions of droperidol described in his paper. Thus throughout the following work the activity of droperidol solvent has been carefully examined.

METHODS

Assessment of analgesia.

Groups of 12 male and female mice (20–30 g) of the Alderley Park strain were used. Two analgesic testing methods were used.

Writhing test. Writhing was induced by the intraperitoneal injection of 0.5% acetic acid and the number of writhes in the following 20 min period was counted. Drugs or saline were injected subcutaneously before the acetic acid. Results were expressed as percentage inhibition of writhing compared with concurrently tested mice injected with saline as a control. This is one of the most sensitive tests for analgesic activity but drugs other than analgesics also inhibit writhing. In this test the activity of droperidol was compared with that of a known analgesic, morphine, a local anaesthetic, lignocaine, and an antihistamine, promethazine.

Hot plate test. This test is less sensitive than the writhing test for detecting analgesic activity. A tenfold increase in dose is necessary to obtain a significant response on the hot plate test compared to the writhing test. However, it is relatively selective for analgesic activity.

The hot plate reaction time test was used as described by Bousfield and Rees (1969). Each mouse was placed in a Perspex open-ended cylinder on a plate the temperature of which was maintained at 55°C. The end point was taken as the time at which there was a distinct shake of the hind paw or a jump...
from the surface of the plate. The reaction time was measured in sec from the initial contact with the plate to the end point. In order to avoid tissue damage, any mouse not responding in 45 sec was removed from the plate.

Reaction times were measured at 10 min intervals after the injection of drug and continued until the results were not significantly different from those obtained from mice in a control group which had been injected with saline.

The drugs tested were, droperidol, fentanyl, mixtures of droperidol and fentanyl, solvent, lignocaine and promethazine.

**Respiratory rate.**

Respiratory rate was measured just before each measurement of hot plate reaction time. The mouse's snout was held in the barrel of a 2 ml syringe. The nozzle of the syringe was connected to a pressure transducer, and pen recorder (Devices Ltd).

**Antagonism of acetylcholine and histamine.**

Guineapig ileum was suspended in Krebs solution at 37°C under tension of 1 g and bubbled with 5% carbon dioxide in oxygen. Changes in tension were measured with a strain gauge transducer (Ether Ltd) connected to a pen recorder (Control Instruments Ltd).

Dose-response curves were obtained for either acetylcholine or histamine alone and in the presence of increasing concentrations of droperidol or its solvent. The experiment was repeated at least 6 times for each agonist.

**Local anaesthetic activity.**

The guineapig weal test (Bulbring and Wajda, 1945) was used. The backs of the guineapigs were shaved on the day before the test. Intradermal weals were raised with 0.1 ml of either droperidol, lignocaine, droperidol solvent or saline. The responses of the guineapig to pin pricks in the centre of each weal were noted, at 5 min intervals, over a 1 hr period.

Unless otherwise stated results are expressed as mean (± standard error). Significance was determined using the Student *t* test.

**RESULTS**

**Writhing test.**

Droperidol, morphine sulphate, lignocaine hydrochloride and promethazine hydrochloride all inhibited the writhing response in a dose-dependent manner (fig. 1). Droperidol was approximately equipotent to morphine in this test and more potent on a mg basis than lignocaine and promethazine. Droperidol solvent showed no detectable activity in this test.

**Hot plate reaction time test.**

Lignocaine and promethazine had no activity in this test. Droperidol in doses up to 20 mg/kg did not increase reaction times above control levels.

Fentanyl 0.1 mg/kg caused a small increase in reaction time of short duration. Fentanyl 0.2 and 0.4 mg/kg induced progressively greater increases in reaction time, the maximum effect with the higher dose being 19.0 sec (±2.0). Administration of droperidol 5 mg/kg with fentanyl caused a significant increase in the maximum hot plate reaction time obtained (P<0.001), and a prolongation of the action of the action of fentanyl. This is best illustrated by noting the response to fentanyl 0.1 mg/kg (fig. 2); the addition of droperidol 5 mg/kg increased the duration of action of fentanyl from 15 to 50 min. In the presence of droperidol the higher doses of fentanyl induced increases in reaction time above the arbitrary cut-off time of 45 sec.

**Respiratory rate.**

Droperidol in doses up to 20 mg/kg had no detectable activity on the respiratory rate of the mouse.

Fentanyl 0.1 mg/kg had no significant action on respiratory rate, but fentanyl 0.2 and 0.4 mg/kg caused dose-dependent depression of rate. Ten min
The effects of droperidol and fentanyl alone and in combination on mouse hot plate reaction time are shown in Fig. 2. The time course of these effects is as follows:

- **(C)** Saline
- **(D)** Droperidol 5 mg/kg
- **(F)** Fentanyl 0.1 mg/kg
- **(D) and (F)** Mixture of fentanyl 0.1 mg/kg and droperidol 5 mg/kg

Each point represents the mean of at least 12 readings. For clarity, only two standard errors are shown.

After injection of fentanyl 0.4 mg/kg, the mean respiratory rate of a group of 16 mice was 118 (±3.6) b.p.m. compared with 190.7 (±7.3) for the group that were given injection of saline.

Mixtures of fentanyl with droperidol 5 mg/kg induced a significantly lower respiratory rate (P<0.05). In the presence of droperidol even 0.1 mg/kg caused a depression of respiratory rate lasting for 60 min (Fig. 3). Neither alone nor in combination with fentanyl, did droperidol solvent affect respiratory rate.

Local anaesthetic activity.

No local anaesthesia was obtained with either saline or solvent. Both lignocaine 0.1% and droperidol 0.1% caused reversible local anaesthesia lasting 40 min in the case of lignocaine and 50 min in the case of droperidol. On the following day it was noted that the sites of droperidol injection were visible as necrotic patches.

**Antagonism of histamine and acetylcholine.**

Droperidol, but not its solvent, antagonized the actions of both histamine and acetylcholine on the isolated guineapig ileum preparation. The effect of increasing concentrations of droperidol on histamine and acetylcholine dose-response curves are shown in figures 4a, b. Up to a concentration of 500 ng/ml, droperidol caused an approximately parallel shift to the right of the histamine dose-response curve. Higher concentrations caused a progressive reduction in the slope of the histamine dose response curve with diminution of the maximum response. The histamine response curves in the presence of droperidol 500 ng/ml and below were used to calculate the PA2 value (Schild, 1947) for droperidol against histamine. This scale was devised by Schild for comparing the potency of antagonists in which the negative logarithm of the concentration of antagonist was taken, i.e. \(\log [1 / \text{antagonist}]\) where \(x\) refers to the ratio of equi-effective doses of agonist before and in the presence of the antagonist; he expressed this as \(PA_x\). If the concentration of antagonist is such that twice the dose of agonist is required to reproduce the original response then the negative logarithm of this concentration is the \(PA_x\) value. The \(PA_x\) value was obtained used the method of Arunlakshana and Schild (1959). The use of this method has been previously described in this journal (Pleuvry and Hunter, 1968).

Six experiments gave a mean \(PA_x\) value (± standard deviation) of 6.12 (±0.36). This shows weak antagonist activity compared with promethazine the \(PA_x\) value of which is 9.14.

Concentrations of droperidol above 500 ng/ml were necessary to cause significant inhibition of acetylcholine responses and diminution of the slope and maximum of the acetylcholine dose response curves occurred with all concentrations of droperidol. This precluded the calculation of the \(PA_x\) value.

**Discussion**

In the doses used the solvent of droperidol has no pharmacological activity relevant to the aspects of
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Fig. 4. Effects of increasing concentrations of droperidol on the response of the guineapig ileum preparation to agonists.

(a) Histamine. (b) Acetylcholine.

C = control dose response curve for each agonist in the absence of droperidol. Subsequent dose response curves were obtained in the presence of droperidol, the dose in ng/ml being shown beside each curve.

the pharmacology of droperidol described in this paper.

Initially droperidol was shown to be active in the mouse writhing test, but this does not necessarily mean that droperidol has analgesic activity. Further investigation of higher doses of droperidol, using the more specific hot plate test, failed to demonstrate any analgesic activity for droperidol administered alone.

However, when droperidol was administered with fentanyl in the ratio of 50:1, potentiation of the analgesic action of fentanyl was observed, in mice. Similar findings have been reported in man by Foldes et al. (1964) who assessed the response to a painful stimulus (towel clip on skin) of anaesthetized patients 12 min after injection of either fentanyl or a mixture of fentanyl and droperidol. Potentiation of fentanyl analgesia by droperidol would be a desirable side effect in the use of the drug mixture. Less desirable, if it occurs in man, would be the concurrent potentiation of the respiratory depression caused by fentanyl as demonstrated, in mice, in this study.

Antagonism of the actions of histamine by droperidol has been demonstrated previously on the rabbit ear artery preparation by Puddy (1971). Two additional pieces of information have been obtained from the present work. First, on the guineapig ileum preparation, histamine appears to have some selective antihistaminic activity, but it is considerably less potent in this respect than promethazine. This point is important because droperidol was shown to be more potent than promethazine in the writhing test, thus indicating that the action of droperidol in the writhing test is not related solely to antihistaminic properties. The second piece of information is that the antagonism of both histamine and acetylcholine by droperidol is not competitive in nature. This is shown by the observation that increasing concentrations of droperidol caused progressive flattening of the agonist dose-response curve and diminution of the maximum. Even low concentrations of droperidol against histamine fulfilled none of the criteria of competitive antagonism described by Arunlakshana and Schild (1959).

The final possibility which could explain the activity of droperidol in the writhing test is local anaesthetic activity. In this study droperidol was found to be equipotent with lignocaine as a local anaesthetic in the guineapig. Local anaesthetic activity has previously been demonstrated for another butyrophenone, haloperidol, by Duxbury (1969). Although entirely reversible as a local anaesthetic on the day of test, droperidol injection sites were visible.
as necrotic patches the next day. Thus the suggestion by Puddy (1971) that it could be used as a local anaesthetic prior to venepuncture should be treated with caution.

The action of droperidol in the mouse writhing test and the antagonism of spasmogens on the guineapig intestine, described in this paper, may be explained in part by the local anaesthetic properties of droperidol. A similar explanation could be applied to the results described by Puddy (1971).

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REFERENCES


