ANALGESIC ACTIVITY OF A NEW QUINOLINE DERIVATIVE RO—4—1778.

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A new analgesic Ro—4—1778 has been studied in rats and its analgesic activity has been compared with that of morphine. The analgesic activity of Ro—4—1778 and morphine was potentiated by chlordiazepoxide.

Analgesic drugs are extensively used in clinical practice. Many new drugs have entered the armamentarium of a clinician for relief of pain. But as yet, no single drug satisfies all the requirements of an ideal analgesic.

Evaluation of analgesic activity of any new compound can best be done on pathological or postoperative pain in patients (Beecher, 1957). However, induced pain in the laboratory animals or human volunteers has often been used as a preliminary investigation. Although such methods have obvious limitation, they are extensively used for screening a new drug to obtain a comparative data on its analgesic activity.

In the present study a new analgesic Ro—4—1778 (1—(p—chlorophenethyl)—6, 7—dimethoxy—2—methyl 1, 2, 3, 4, tetrahydro isoquinoline has been studied for its analgesic action in rats. The drug is a quinoline compound and was synthesised by Brossi *et al* (1960). This drug has been compared with morphine. Further, it has also been studied in combination with chlordiazepoxide (Librium). Thermal stimulus was used for producing pain and a graded response method was employed for evaluating the analgesic activity.

METHODS

The analagesic activity was determined in rats using the Techno Analgesiometer (Techno Electronics, Lucknow). The rat was kept in the holder, the tail resting on a bridge with an electrically heated tantalum wire. The tail received radiant heat from wire. The wire was heated by putting on the instrument and a current strength of 8 m A was passed and the time taken for withdrawal of the tail was noted. This gave the normal or control reading. Three control readings were taken. The drug was then injected intraperitoneally and the effect was noted at the end of 45 min, by taking

three readings as before. An increase in time over control was an index of the analgesia produced by the drug. If, however, a rat failed to withdraw its tail within 15 sec. test reading was recorded as more than 15 sec. A maximum time limit of 15 sec was found necessary since it was observed that if the tail was allowed to rest on the bridge beyond 15 sec it got burnt in most of the cases and the rat could not be used again. In a group that received chlordiazepoxide, it was given along with the analgesic intraperitoneally.

As far as possible the same rats were used for all the doses of each drug. However, if, the rats were found unsuitable for repeated studies they were replaced by fresh ones.

RESULTS

Initially the effect of normal saline intraperitoneally was studied in six rats. There was no change in pain threshold after saline. Ro—4—1778 and morphine in four different doses with and without chlordiazepoxide were studied and the results are given in the Tables I & II. The number of rats receiving each dose ranged between 5 and 15.

Morphine was used in doses of 2.5, 5.0, 10.0 and 12.5 mg per kg respectively. In each case, pain threshold was modified. It was significantly increased with a dose of 5 mg and above ($P<0.05$).

Ro-4-1778 was used in doses of 10, 20, 30 and 50mg/kg. Here a definite analgesic activity was noted with a dose of 20 mg and above ($P<0.01$) (Table No. II).

It was noted further that in a few rats receiving Ro-4-1778 a dose higher than 50 mg/kg showed an evidence of hyperexcitability and some actually went into convulsions. Five rats receiving a dose of 100 mg/kg died of severe clonic convulsions.

Chlordiazepoxide alone was given in 3 rats in 2 doses 5 mg and 10 mg/kg. There was no evidence of any analgesia. Hence it was thought worth while to see if a dose of 10 mg/kg of the drug would have any effect on morphine and Ro-4-1778 induced analgesia. It may be seen from the Tables I & II that the analgesic effect was potentiated by chlordiazepoxide in case of both the drugs.

Log dose response curves were drawn as shown in fig. I. It will be seen that both drugs gave a fairly good dose response curve. However, morphine is much more potent than Ro-4-1778.

TABLE I

Effect of Morphine alone and in combination with chlordiazepoxide

Dose of morphine	Morphine			Morphine + chlordiazepoxide 10 mg/kg		
	Before	After	% Increase	Before	After	% Increase
2.5 mg/kg	6.8 ± 0.46	9.0 ± 1.32	32.3 t= 1.57 p< 0.20	6.0 ± 0.40	13.3 ± 0.80	121.7 t= 8.17 p< 0.01
5 mg/kg	6.8 ± 0.27	11.7 ± 0.85	72.0 t= 2.07 p< 0.05	6.8 ± 0.41	14.2 ± 0.43	108.8 t= 12.36 p < 0.01
10 mg/kg	6.2 ± 0.23	12.3 ± 1.60	98.4 t= 3.69 p< 0.01	6.7 ± 0.50	15.0 ± 0.00	123.9 t= 16.5 p < 0.01
12.5 mg/kg	6.4 ± 0.30	13.8 ± 0.83	115.6 t= 8.4 p< 0.01			

Before and after refer to the mean reading in sec required for the tail to be moved before and after the drug

± Refers to the standard error

TABLE II

Effect of Ro-4-1778 alone and in combination with chlordiazepoxide

Dose of Ro-4-1778	Ro-4-1778			Ro-4-1778 + chlordiazepoxide 10 mg/kg		
	Before	After	% Increase	Before	After	% Increase
10 mg/kg	6.6 ± 0.58	7.7 ± 0.59	16.7 t= 1.33 p <0.20	6.6 ± 0.53	8.8 ± 0.79	33.3 t= 2.31 p <0.05
20 mg/kg	5.9 ± 0.15	10.9 ± 0.96	84.7 t=16.34 p <0.01	6.8 ± 0.29	13.8 ± 0.80	102.9 t= 8.32 p < 0.01
30 mg/kg	6.8 ± 0.23	13.6 ± 0.56	100.0 t= 35.7 p <0.01	7.0 ±0.27	14.7 ± 0.21	110.0 t=22.28 p <0.01
50 mg/kg	6.2 ± 0.86	15.0 ±0.00	141.9 t= 10.23 p <0.01			

Before and after refer to the mean reading in sec required for the tail to be moved before and after the drug

± Refers to the standard error

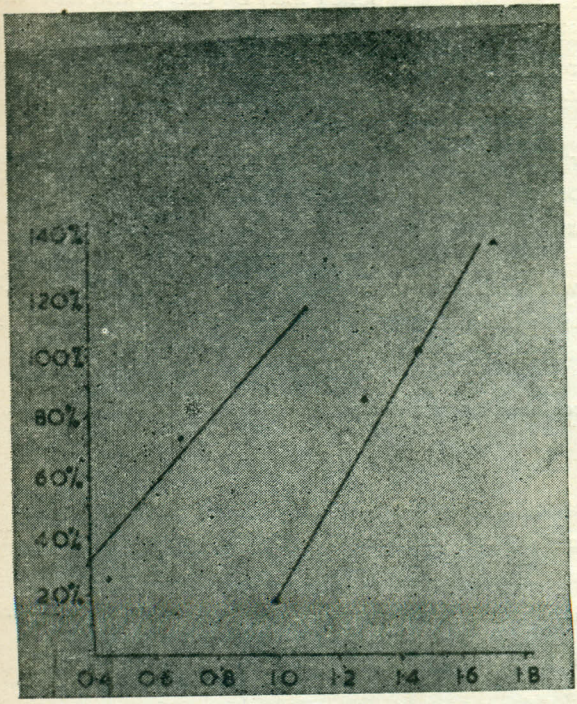

Fig. 1. Dose response curves : Abscissa showing logarithm of the dose, ordinate% increase in threshold with—Morphine and—Ro-4-1778.

DISCUSSION

From the dose response curves it is clear that the analgesic potency of the drug Ro-4-1778 is less than that of morphine. The two dose-response lines are not parallel and therefore, at ED 50 ratio is calculated for comparision of potency of the two drugs. On the basis of this ratio it is seen that morphine is about 4.5 times more potent than Ro-4-1778. The dose response lines are not parallel and it, therefore, appears that the two drugs are producing action by different mechanism or at least by acting at different sites.

Courvoisier *et al.*, (1953) demonstrated that chlorpromazine potentiates the analgesic effect of morphine and pethidine in mice. It is therefore interesting to note that chlordiazepoxide a non-phenothiazine tranquilliser also has similar effeet in doses in which it fails to show any analgesic action.

From the Table I, it is found that 10 mg chlordiazepoxide when combined with morphine 2.5 mg and 5 mg/kg produced an increase in time by 121.7 per cent and 108.8 respectively (the difference however is not statistic-

ally significant). This discrepency may be due to the fact that when a fixed dose of chlordiazepoxie 10 mg/kg is combined with morphine, it is immaterial whether 2.5 or 5 mg/kg is administered since even with 2.5 mg/kg nearly a maximal effect is produced).

Similarly from Table II, it is evident that chlordiazepoxide is more effective in potentiating the analgesic effect of lower doses of Ro-4-1778 i.e, 10 mg & 20 mg/kg.

Since it was found that the analgesic action of Ro-4-1778 was increased when combined with Chlordiazepoxide, it was thought to give a clinical trial of the combination in postoperative patients.

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