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ANALGESIC AND OTHER PROPERTIES OF MORPHOLINOETHYLNORPETHIDINE

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Millar and Stephenson (1956) have investigated the analgesic action of a series of aminoalkyl derivatives of pethidine prepared by Anderson, Frearson, and Stern (1954, private communication). The most powerful of these compounds was morpholinoethylnorpethidine hydrochloride (TA1) with an analgesic activity of at least three times that of pethidine in rats. Further properties of this compound are reported here.

METHODS

The same procedures have been used to test effects on pain threshold, respiration, and rectal temperature as in the investigation of other analgesics in this laboratory (Green and Young, 1951; Green, 1953). The analgesic estimates in Table I were derived by quantal analysis of a test in which pain thresholds to heat and to pressure were measured 30 min. after subcutaneous injection of TA1 and morphine at each of three dose levels in groups of ten 3–4-week-old Wistar rats. Respiratory frequencies were determined at the same time as the pain threshold measurements. Effects on the cough reflex in anaesthetized cats and antagonism by nalorphine of the analgesic and respiratory depressant properties were determined by the methods used by Green and Ward (1955) and Green, Ruffell, and Walton (1954) respectively.

RESULTS

Analgesia.—TA1 was capable of causing as great an elevation of pain threshold as morphine in rats, and its relative potency by subcutaneous injection was intermediate between that of morphine and pethidine in this species (Table I). This is probably also true by subcutaneous injection in dogs, since 5 mg./kg. TA1 elevated the pain threshold by at least 100% and caused moderate narcosis in five of six dogs and since its intensity and duration of action were comparable with those previously found (Green, 1953) with 1–2 mg./kg. morphine sulphate or 20 mg./kg. pethidine hydrochloride. Argent (1955, private communication) has found that in man, too, the activity of the morpholino compound is greater than that of pethidine and less than that of morphine.

TABLE I

DOSES RAISING THE PAIN THRESHOLD TO HEAT AND TO PRESSURE BY AT LEAST 100% IN 50% OF RATS (ED50), AND RELATIVE ANALGESIC POTENCIES

The limits of error, $P=0.95$, are shown in parentheses

	ED50 (mg. kg.)		Relative Potency	
	Heat	Pressure	Heat	Pressure
TA1	5·2 (2·9–9·1)	2·6 (1·7–4·0)	0·58 (0·31–1·1)	0·54 (0·28–1·0)
Morphine sulphate	3·0 (2·3–4·0)	1·4 (0·86–2·2)	1·0	1·0
Pethidine hydrochloride			0·2*	0·27*

* Comparative estimates of Green and Young (1951).

In each of two cats 2.5 mg./kg. TA1 caused mydriasis and slight analgesia, but three hours later, when the cats had apparently fully recovered, a further dose of 10 mg./kg. caused marked excitement.

Toxicity and Respiratory Depression.—The acute intravenous LD50 of TA1 in mice was approximately 45 mg./kg. Unlike pethidine it did not cause violent convulsions. Respiratory depression seemed to be its main toxic action in this species and also in rats, rabbits, cats and dogs. Other signs in mice included such morphine-like effects as tail erection, analgesia, mydriasis, and bursts of hyperactivity.

The mean respiratory frequencies of groups of 10 rats 30 min. after subcutaneous injection are plotted against the dose of the analgesics in Fig. 1. Relative to its analgesic activity in this species, the respiratory depressant action of TA1 is not significantly different from that of morphine. The respiratory minute volume was depressed by at least 70%, largely by reduction of frequency, after 15 mg./kg. TA1 subcutaneously in each of

five rabbits. In normal dogs the frequency of breathing was slowed after 5 mg./kg. TA1 subcutaneously, and in a dog anaesthetized with pentobarbitone sodium (40 mg./kg.) the rate was reduced from 16/min. to 10/min., for several minutes after 1 mg./kg. intravenously. In each of two cats, 1 and 3 mg./kg. intravenously reduced the rate by about 30% and 50% respectively.

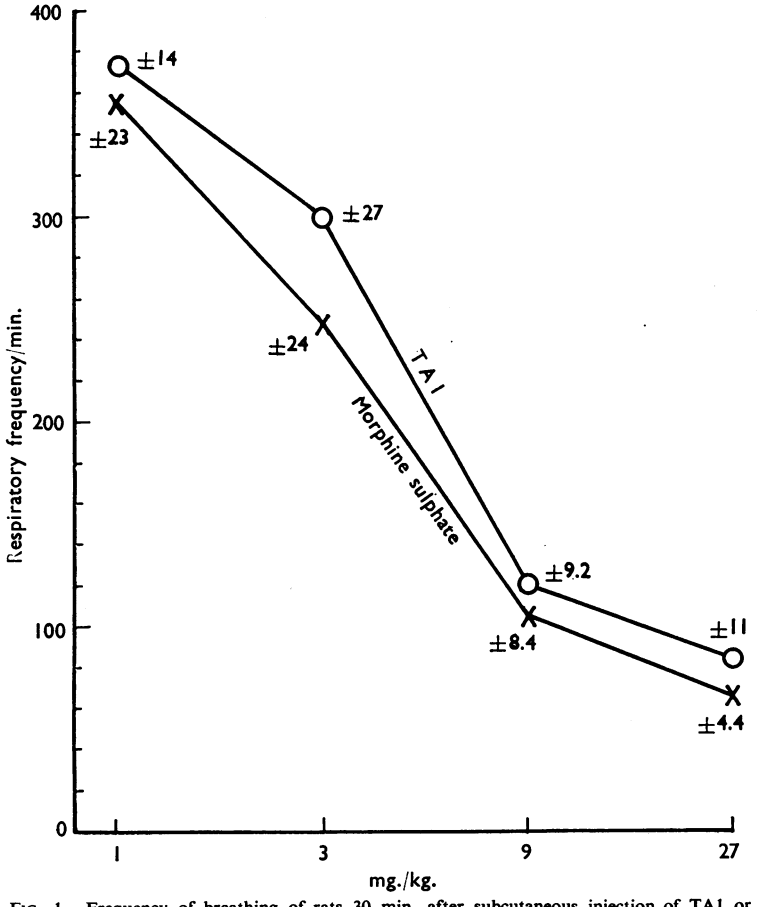

FIG. 1.—Frequency of breathing of rats 30 min. after subcutaneous injection of TA1 or morphine sulphate. Means for groups of ten rats and standard errors. Controls 376±18.

Antitussive Action.—Coughs caused by electrical stimulation of the superior laryngeal nerve were reduced in intensity by 0.3 mg./kg. and abolished by 1 mg./kg. TA1 in each of two anaesthetized cats; in one of these animals coughs caused by mechanical irritation or SO_2 were similarly affected. Pethidine (1–3 mg./kg.) and morphine (0.3–1.0 mg./kg.) have produced effects comparable with this (Green and Ward, 1955).

Temperature.—After 8 mg./kg. TA1 subcutaneously the fall in rectal temperature of 2 rabbits was slightly greater, but of shorter duration, than that after 4 mg./kg. morphine sulphate in 2 other rabbits.

Gastro-intestinal Effects.—Unlike morphine, but in common with many synthetic analgesics, TA1 was not emetic in dogs, but salivation and defaecation occurred in 4 of 6 dogs soon after the subcutaneous injection of 5 mg./kg. As with other morphine-like analgesics TA1 inhibited the peristaltic reflex of isolated guinea-pig ileum, the inhibition being partial at 3×10^{-7} and complete at 10^{-6}. Concentrations of 10^{-6} did not prevent acetylcholine (5×10^{-7}) or histamine (5×10^{-7}) from causing maximal contractions of isolated guinea-pig ileum.

Cardiovascular Effects.—Slight bradycardia and a fall of 30 mm. Hg in the mean carotid blood pressure occurred after intravenous injection of 1 mg./kg. TA1 in a dog anaesthetized with pentobarbitone sodium. A dose of 3 mg./kg. reduced the heart rate from 170/min. to 45/min. and lowered the mean carotid blood pressure by 40 mm. Hg. The bradycardia and the fall in blood pressure were abolished by atropine (0.1 mg./kg.), and so, as with morphine, these actions are presumably due to vagal excitation. After atropinization, doses of 10–40 mg./kg. TA1 reduced blood pressure without slowing the heart.

Action on the Pupil.—As with other morphine-like analgesics, TA1 caused mydriasis in mice and cats and myosis in dogs.

Antagonism by Nalorphine.—Nalorphine inhibited several of the morphine-like properties of TA1. Analgesia caused by large doses (25 mg./kg.) of TA1 in rats was very greatly reduced by as little as 1 mg./kg. nalorphine (Table II), and

the respiratory frequency in these animals was restored to normal. Respiratory minute-volume, depressed after 15 mg./kg. TA1 subcutaneously in rabbits, was restored to normal by 0.5 mg./kg. nalorphine intravenously in each of five animals. The suppression of the cough reflex and the reduction in respiratory frequency caused by 3 mg./kg.

TABLE II

ANTAGONISM OF THE ANALGESIC ACTION OF TA1 BY NALORPHINE HYDROCHLORIDE IN RATS

The pain thresholds were measured 30 min. after subcutaneous injection of the drugs

		Incidence of a 100% Rise in Threshold		ED50 of Nalorphine and Limits, $P=0.95$ (mg./kg.)	
TA1 (mg./kg.)	Nalorphine (mg./kg.)	Heat	Pressure	Heat	Pressure
25	0	10/10	10/10		
25	0·25	10/10	10/10	0·99 (0·57–1·7)	2·6 (1·2–5·3)
25	1·0	4/10	7/10		
25	4·0	1/10	4/10		

TA1 in two anaesthetized cats were antagonized by 0.3 mg./kg. nalorphine. The morphine-like excitement caused by 10 mg./kg. TA1 in non-anaesthetized cats was also abolished by 2 mg./kg. nalorphine intraperitoneally. Similarly, whereas the peristaltic reflex of isolated guinea-pig ileum was, in the absence of nalorphine, abolished by TA1 at 10^{-6}, as much as 10^{-5} was required to cause inhibition in the presence of 10^{-7} nalorphine.

Chronic Toxicity.—Daily subcutaneous injection of 10 mg./kg. TA1 in newly weaned rats for 9 weeks caused only a very slight retardation of growth and no change in the histological appearance of the lungs, livers, spleens, or kidneys.

SUMMARY

1. Morpholinoethylnorpethidine is a powerful analgesic, and its activities in rats and dogs are intermediate between those of pethidine and morphine.

2. This new compound depressed respiration in several species ; in rats this action was as powerful, relative to its analgesic potency, as that of morphine. Its actions on the cough reflex in anaesthetized cats, on rectal temperature in rabbits, on pupil diameter in mice, cats and dogs, and on heart rate in dogs also resembled those of morphine. Similarly it abolished the peristaltic reflex of isolated guinea-pig ileum and caused defaecation in dogs. In cats it produced morphine-like excitement.

3. Its effects on pain threshold, respiration, and the cough and peristaltic reflexes were antagonized by nalorphine.

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