Dopaminergic potency of apomorphine homologues in mice with unilateral lesions of the caudate nucleus

J. PEARL, *Sterling-Winthrop Research Institute, Rensselaer, New York* 12144, *U.S.A.*

The *N*-propyl homologue of apomorphine appeared to be more potent than apomorphine in improving symptoms of parkinsonism in man (Cotzias, Papavasiliou & others, 1976). Likewise, the *N*-propyl homologue was more potent than apomorphine in producing postural asymmetries in mice (Ginos, Cotzias & others, 1975; Pearl, Schumann & Wood, 1976) and rats (Neumeyer, Dafeldecker & others, 1977) with unilateral lesions of the nigrostriatal system. The dopaminergic potency of several apomorphine homologues in mice with unilateral lesions of the caudate nucleus has now been assessed and the results compared with those of others who used different indicants of dopaminergic activity.

Male Swiss-Webster mice (Taconic Farms, N.Y.), 20–23 g at the time of lesioning and 36–45 g at testing, had unilateral lesions of the caudate nucleus made by suction according to Lotti (1971).

Drugs were dissolved in water, and oral, intraperitoneal and subcutaneous medications were 0·01 ml g^{-1}. Observations, 2 min maximum duration, took place immediately before and 15, 30, 60, 120 and 240 min after medication. None of the mice exhibited postural asymmetry toward the lesioned side before medication. Mice were scored positive if they showed postural asymmetry toward the lesioned side during any of the observation period after medication. The ED50 values in mg kg^{-1} of free base were calculated with a computer according to the quantal method described by Finney (1964). At least three doses of each drug were used to estimate ED50 values.

Table 1. *Potency of apomorphine homologues in mice with unilateral lesions of caudate nucleus*[a].

N-substituent	ED50 (95% limits) in mg kg^{-1} base	Slope	Potency ratio
	Oral		
n-Propyl	0·63 (0·19–2·08)	2·5[b]	44
Ethyl	9·88 (8·41–11·5)	9·6	3
Methyl	27·8 (21·3–36·3)	6·2	1
n-Butyl	Inactive 50	—	—
	Intraperitoneal		
n-Propyl	0·034 (0·028–0·040)	10·7[c]	27
Ethyl	0·088 (0·023–0·12)	3·1	10
Methyl	0·92 (0·82–1·09)	6·0	1
n-Butyl	Inactive 6·4	—	—
	Subcutaneous		
n-Propyl	0·014 (0·010–0·019)	5·7	16
Methyl	0·23 (0·22–0·26)	12·1	1
n-Butyl	Inactive 100	—	

[a]Mice were observed from 15 to 240 min after medication for postural asymmetries directed toward the side of the lesion. The data for the propyl and methyl compounds were reported previously (Pearl & others, 1976).

[b]The slope of the propyl compound was significantly different from those of the ethyl and methyl compounds ($P<0.05$).

[c]The slope of the propyl compound was significantly different from that of the ethyl compound ($P<0.05$).

Apomorphine HCl was kindly donated by Merck Sharp and Dohme Research Laboratories. The three apomorphine homologues came from Sterling-Winthrop Research Institute: *N*-ethylnorapomorphine HCl, *N*-n-propylnorapomorphine HCl, *N*-n-butylnorapomorphine HCl. Because all of the compounds were derived from morphine, they belong to the (*R*) - (−) series (Atkinson, Bullock & others, 1975).

Table 1 shows the ED50 values of the drugs and their potency ratios relative to apomorphine. Potency increased as the *N*-carbon chain length increased, reached maximum at propyl and vanished at butyl: propyl > ethyl > methyl (apomorphine) > butyl.

Table 2 shows the effects of the three active compounds at different intervals after medication. The peak effect appeared to be 15 min after subcutaneous and intraperitoneal injection of the compounds and from 15 to 30 min after oral medication. At the time of peak effect the ED50 values of the compounds were virtually identical to the ED50 values shown in Table 1. At equiactive doses no appreciable difference in duration of activity of the compounds was evident.

Results for the dopaminergic potency of the apomorphine homologues agree with some of but not all of the previous results. The butyl homologue was consistently inactive in producing postural asymmetries in lesioned mice (present study) and in producing emesis in dogs (Atkinson & others, 1975).

The ethyl homologue was consistently more potent than apomorphine in producing postural asymmetries in lesioned mice (present study), gnawing in mice (Koch, Cannon & Burkman, 1968) and emesis in dogs (Atkinson & others, 1975; Koch & others, 1968). The ethyl homologue was more potent than the propyl homologue in producing emesis in dogs (Atkinson & others, 1975; Koch & others, 1968) and gnawing in mice (Koch & others, 1968) but not in producing asymmetries in mice with unilateral lesions of the caudate nucleus (present study).

The propyl homologue was more potent than apomorphine in producing postural asymmetries in mice with unilateral caudate lesions made by suction (Ginos & others, 1975; Pearl & others, 1976) and in rats with substantia nigra lesions made by electrolytic

Table 2. Effects of apomorphine homologues in caudate-lesioned mice at different time intervals after medication.

N-substituent	Dose mg kg^{-1} base	No. mice tested	% of mice responding at time in min after dose				
			15	30	60	120	240
		Oral					
n-Propyl	0·2	6	0	0	0	0	0
	0·4	12	43	43	25	0	0
	0·8	8	50	50	37	37	37
	1·0	4	75	75	50	25	0
	1·6	12	75	75	75	33	33
Ethyl	5	4	0	0	0	0	0
	10	4	50	50	50	0	0
	12	5	80	80	80	20	0
	20	4	100	100	100	10	0
Methyl	16	12	8	8	8	8	0
	32	10	60	60	40	30	20
	64	12	93	100	93	75	17
		Intraperitoneal					
n-Propyl	0·025	8	12	12	0	0	0
	0·035	10	50	50	30	0	0
	0·05	8	100	87	25	0	0
Ethyl	0·05	4	25	25	0	0	0
	0·10	4	50	25	0	0	0
	0·17	6	83	83	17	0	0
Methyl	0·4	8	0	0	0	0	0
	0·8	8	25	12	12	0	0
	1·1	10	50	30	0	0	0
	1·6	8	100	75	37	0	0
		Subcutaneous					
n-Propyl	0·01	10	20	10	0	0	0
	0·02	10	80	80	20	0	0
	0·04	5	100	100	20	0	0
Methyl	0·125	5	0	0	0	0	0
	0·25	12	67	67	0	0	0
	0·5	5	100	100	0	0	0

coagulation or by 6-hydroxydopamine (Costall, Naylor & Neumeyer, 1975; Mendez, Cotzias & others, 1975; Neumeyer & others, 1977), and stereotyped biting in rats (Costall & others, 1975; Schoenfeld, Neumeyer & others, 1975). Whilst the propyl homologue, orally, was more potent than apomorphine in producing postural asymmetries in mice with caudate lesions induced by 6-hydroxydopamine, this was not so when the aporphines were given subcutaneously (Pearl & others, 1976), whilst the propyl analogue was more potent than apomorphine in producing stereotyped biting in monkeys (Atkinson & others, 1975) and in rats (Costall & others, 1975) this was not evident for stereotyped sniffing in rats (Costall & others, 1975) or gnawing in mice (Koch & others, 1968), and whilst in one study the propyl homologue was a more potent emetic than apomorphine in dogs (Atkinson & others, 1975), this was not so in another study (Koch & others, 1968). Further, the propyl homologue, injected into various regions of rat brain, was not substantially more potent than apomorphine in producing biting (Costall, & others, 1975) and, *in vitro*, not more potent than apomorphine in stimulating striatal adenylate cyclase (Miller, Kelly & Neumeyer, 1976).

Concerning the interpretation of differences in potency between apomorphine and its homologues, several considerations may be applicable. For example, the lipophilic nature of the propyl homologue may enhance entry into brain (Burkman, Notari & Van Tyle, 1974). That the propyl homologue was more potent than apomorphine in some of but not all of the tests of dopaminergic activity may point to the existence of different types of dopamine receptors in the extrapyramidal as opposed to other areas of the brain (Cools & van Rossum, 1976; Neumeyer & others, 1977).

June 20, 1977

REFERENCES

ATKINSON, E. R., BULLOCK, F. J., GRANCHELLI, F. E., ARCHER, S., ROSENBERG, F. J., TEIGER, D. G. & NACHOD, F. C. (1975). *J. medl Chem.*, **18**, 1000–1003.

BURKMAN, A. M., NOTARI, R. E. & VAN TYLE, W. K. (1974). *J. Pharm. Pharmac.*, **26**, 493–507.

COOLS, A. R. & VAN ROSSUM, J. M. (1976). *Psychopharmacologica*, **45**, 243–254.

COSTALL, B. A., NAYLOR, R. J. & NEUMEYER, J. L. (1975). *Eur. J. Pharmac.*, **31**, 1–16.

COTZIAS, G. C., PAPAVASILIOU, P. S., TOLOSA, E. S., MENDEZ, J. S. & BELL-MIDURA, M. (1976). *New Engl. J. Med.*, **294**, 567–572.

FINNEY, D. J. (1964). *Statistical Methods in Biological Assay*, 2nd ed, New York: Hafner Publishing Co.

GINOS, J. Z., COTZIAS, G. C., TOLOSA, E., TANG, L. C. & LO MONTE, A. (1975). *J. medl Chem.*, **18**, 1194–1200.

KOCH, M. V., CANNON, J. G. & BURKMAN, A. M. (1968). *Ibid.*, **11**, 974–981.

LOTTI, V. A. (1971). *Life Sci.*, **10**, 781–789.

MENDEZ, J. S., COTZIAS, G. C., FINN, B. W. & DAHL, K. (1975). *Ibid.*, **16**, 1737–1742.

MILLER, R. J., KELLY, P. H. & NEUMEYER, J. L. (1976). *Eur. J. Pharmac.*, **35**, 77–83.

NEUMEYER, J. L., DAFELDECKER, W. P., COSTALL, B. & NAYLOR, R. J. (1977). *J. medl Chem.*, **20**, 190–196.

PEARL, J., SCHUMANN, A. & WOOD, G. W. (1976). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **35**, 269.

SCHOENFELD, R. I., NEUMEYER, J. L., DAFELDECKER, W. & ROFFLER-TARLOV, S. (1975). *Eur. J. Pharmac.*, **30**, 63–68.