SHORT COMMUNICATION:

SPASMOLYTIC ACTIVITY OF 3-TROPANYL 2- (P-CHLOROPHENYL) ACRYLATE HYDROCHLORIDE (SK & F 21000)

R.K. MEHTA, P.N. SHRIVASTAVA AND D.N. SHRIVASTAVA

Department of Pharmacology,
College of Veterinary Science and Animal Husbandary, Jabalpur

Summary: The antispasmodic activity of 3-tropanyl 2-(p-chlorophenyl) acrylate hydrochloride (SK & F 21,000), a new synthetic derivative of atropine, was investigated by faecal pellet excretion test and by charcoal meal inhibition test in mice. In both the tests there was dose-dependent inhibition. The ID_{50} values of SK & F 21,000 and atropine in pellet excretion test were 3.735 ± 1.09 *mg/kg* and 1.256 ± 1.12 *mg/kg*, respectively. The ID_{50} of SK & F 21,000 in charcoal meal inhibition test was 3.449 ± 1.04 *mg/kg*. The LD_{50} of SK & F 21,000 was about 14 times less than that of atropine in mice.

Key words: spasmolytic activity SK&F 21000

INTRODUCTION

Atropine the well known antispasmodic produces several undesirable toxic effects, such as mydriasis, dryness of mouth and palpitations. A series of atropine substitutes has been synthesised with the hope of minimising these effects. In the present study the antispasmodic activity of a new compound, 3-tropanyl 2-(p-chlorophenyl) acrylate hydrochloride (SK & F 21,000; Smith Kline & French Labs, Philadelphia) which has chlorine at the para position on the tropic acid radicle of atropine, has been investigated and its activity compared with that of atropine.

MATERIALS AND METHODS

Mice of either sex weighing about 30 g were used for this study.

Acute toxicity: Oral and ip LD_{50} values of aqueous solution of SK & F 21,000 and atropine sulphate were determined by observing the mice for any gross symptoms and for 24 hr mortality. Groups of 4-8 mice received varying doses of the drugs for the determination of LD_{50} values

The faecal pellet inhibition test: The animals were deprived of food for 20 hr. The number of faecal pellets excreted by each animal was counted hourly for 4 hr and again on the second day, when the animals received a fixed dose (ip) of SK & F 21,000 or atropine.

The ID_{50}, (dose inhibiting by 50%, the number of faecal pellets) was calculated as described by Finney (1).

The charcoal inhibition test: The animals deprived of food for 20 hr received a fixed dose of SK & F 21000 (ip). Ten min later, 0. 25 *ml* of 5% suspension of charcoal in 5% gum tragacanth was administered orally to each mouse. Control animals received only the charcoal meal. The mice were killed with ether 30 min after the administration of charcoal meal; the intestine (from pylorus to caecum) was removed and stretched under a load of 3 g for 20 sec in order to obtain uniform elasticity for measurement. The length of small intestine traversed by charcoal was measured. The data were analysed by the method of Turner (5) as modified by Witkin *et al.* (6). The ID_{50}, (the dose inhibiting travel of charcoal meal in gut by 50%) was calculated as described by Finney (1)

RESULTS

The oral and ip LD_{50} of SK & F 21000 were 35.0 *mg/kg* and 17.95±1.08 *mg/kg* respectively. The ip LD_{50} of atropine was 248±1.03 *mg/kg*. Toxic doses of SK & F 21000 in mice caused Straub tail and piloerection accompanied by fast, irregular respiration. This was followed by clonic and finally by tonic convulsions leading to death in about 10-20 min. The animals which survived after a few paroxysms of convulsions or did not show convulsions, were dull and showed decreased motor activity and ataxia.

SK & F 21000 and atropine caused dose-dependent inhibition of excretion of faecal pellets in mice. The ID_{50} of SK & F 21000 and of atropine were 3.735±1.09 *mg/kg* and

TABLE I : Effect of SK & F 21000 and atropine on excretion of faecal pellets in mice.

Drug	*Dose (mg/kg (ip)*	*Mean number of pellets passed in 4 hr**		
		Control	*Treated*	*%inhibition*
Atropine sulphate	0.5	17.3 (8)	13.6 (8)	21.0
	1	17.1 (8)	8.9 (8)	48.2
	2	16.3 (12)	6.3 (12)	61.0
SK & F 21000	2.5	26.1 (8)	16.8 (8)	35.9
	5.0	20.1 (8)	7.4 (8)	63.4
	7.5	24.3 (8)	7.1 (8)	70.6

*Observations were begun immediately after the administration of drugs, to mice fasted for 20 hr.
Number of mice in the group in parentheses.
ID_{50} of SK & F 21000 = 3.735±1.09 *mg/kg*
ID_{50} of atropine sulphate = 1.256±1.12 *mg/kg*

1.256± 1.12 *mg/kg* (Table I). SK & F 21000 also caused dose-dependent inhibition of charcoal meal travel in the gut of mice and the ID_{50} was 3.449±1.04 *mg/kg* (Table II).

TABLE II : Effect of SK & F 21,000 on the charcoal meal travel in the gut of mice.

Dose (mg/ kg, ip)	*Length of intestine (cm) traversed by charcoal at 1/2 hr.*		*Mean inhibition*	*% inhibition*
	Control	*Treated*		
2.5	42.35 (8)	36.44 (8)	5.91	13.9
5.0	47.95 (8)	20.74 (8)	27.21	56.53
7.5	50.5 (8)	11.0 (8)	38.5	78.2

Number of mice in the group in parentheses
ID50 — 3.449± 1.04 mg/kg.

DISCUSSION

The intraperitoneal LD_{50} of SK & F 21000 in mice was 17.95±1.08 *mg/kg* and that of atropine was 248 ±1.03 *mg/kg* which indicates that the new compound is about 14 times more toxic. SK & F 21000 and atropine caused dose-dependent inhibition of excretion of pellets and their ID_{50} values were 3.735±1.09 *mg/kg* and 1.256±1.12 *mg/kg* respectively. SK & F 21000 therefore, appears to be about 3 times less potent than atropine as an antispasmodic.

SK & F 2100 also caused dose-dependent inhibition of charcoal meal travel in the gut of mice and its ID_{50} was 3.449±1.04 *mg/kg* which is quite comparable-to that obtained in faecal pellet inhibition test. The inhibition of gastric emptying in rat by "SK & F 21000 composite" was investigated by studying the passage of amberlite pellet from the stomach and the ED_{50} (dose reducing passage of amberlite pellets from stomach by 50%) was 44 *mg/kg* (2). The difference between ID_{50} values calculated with faecal pellet inhibition test or the charcoal meal test in this study and the ED_{50} in gastric emptying inhibition test (2), may be ascribed to the differences in techniques and species and also to the fact that 50 *mg* of "SK & F 21000 composite" is equivalent to 1 *mg* of the active dose of SK & F 21000.

In mice SK & F 21000 (8 *mg/kg* ip) does not block pilocarpine induced salivation (4), indicating that SK & F 21000 though anticholinergic *in vitro* (3) is devoid of antisialagogue effect of atropine at the anti-spasmodic dose. The superiority of SK & F 21000, however, can be ascertained only after its pharmacodynamic effects are investigated.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. R.L. Kaushal, Dean of the Faculty of Vety. Sci. & A.H., Jabalpur for providing facilities in the laboratory and for his keen interest in the research

work. Thanks are also due to Dr. M. R. Patel, Associate Dean, for his encouragement, and to Shri S.K. Agrawal for his generous help in statistical analysis.

REFERENCES

1. Finney, D.J. Probit Analysis. *A Statistical Treatment of the Sigmoid Curve*, Second edition. p. 20-47, 1952. The Syndics of Cambridge University Press.
2. Joshi, H.L. The effect of 3-tropanyl 2-(p-chlorophenyl) acrylate hydrochloride on gastrointestinal motility and secretion in rat and gastrointestinal motility in sheep. *Ph.D. Thesis, Univ. of Illinois, U.S.A.*, 1969.
3. Mehta, R.K. Quantitative evaluation of antispasmodic activity of 3-tropanyl 2-(p-chlorophenyl) acrylate hydrochloride on smooth muscle preparations. *Ph.D. Thesis, Univ. of Illinois, U.S.A.*, 1969.
4. Mehta, R.K., D.V. Shilaskar, S.M. Ali and I.S. Chhabra. Pharmacological studies of 3-trophanyl 2-(p-chlorophenyl acrylate hydrochloride. Part I — Anti-sialagogue and anti-histaminic activity. *JNKVV, Res. Jour. (Jabalpur)*, **6** : 109-111, 1972.
5. Turner, R.A. *Screening Methods in Pharmacology, Ed. I*, pp. 142. Academic Press, New York and London, 1965.
6. Witkin, L.B., C.F. Huebner, F. Galdi, E.O'keefe, P. Spitaletta and A.J. Plummer. Pharmacology of 2-aminoindane hydrochloride (SU-8629) : A potent-non-narcotic analgestic. *J. Pharmac. Exp. Ther.*, **133** : 400-408, 1961.