

ANTIPYRETIC ACTIVITY OF DIACETYL PARA-AMINO PHENOL

POONAM SEWAK, JYOTI SAXENA,
A. K. DORLE AND J. K. GROVER*

Department of Pharmaceutical Sciences,
University of Nagpur, Nagpur - 440 010

*Department of Pharmacology,
All-India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029

(Received on June 27, 1988)

Abstract : Diacetyl para-amino phenol (DAPAP) was generated by interaction between aspirin and paracetamol in a mechanical shaker. It revealed antipyretic activity in albino rats. The antipyretic action was found to be having the same onset of action and duration as that of aspirin. This compound lacked ulcerogenic and analgesic activity. DAPAP therefore may have safety as an antipyretic drug in patients with history of peptic ulcer.

Key words : diacetyl para-aminophenol ulcerogenic antipyretic and analgesic

INTRODUCTION

Although, it is generally believed that the interaction between aspirin and paracetamol leading to the formation of diacetyl para amino phenol (DAPAP) (1) does not cause loss of therapeutic activity of aspirin, one may expect the compound to be either more or less active than the reactants. Hence, it was thought worthwhile to evaluate DAPAP for antipyretic and ulcerogenic activity in rats.

Preparation and isolation of DAPAP: A 50.50 v/v mixture of methanol and distilled water was employed for the preparation of saturated solutions of aspirin and paracetamol. They were placed in a round bottom flask (ratio of aspirin and paracetamol, 7 : 3). To this was added equal quantity of 20 ml each of acetic anhydride and analytical grade pyridine. This mixture was refluxed on an electrical water bath for three hr and cooled. On cooling

yellowish brown crystals appeared. They were recrystallised in methanol and treated with activated charcoal to give brilliant white crystals of DAPAP (1).

Antipyretic activity : Both acute antipyretic potency and the duration of antipyresis of the interaction product, DAPAP were studied (2) on albino rats. The normal rectal temperature of albino rats of either sex (10-150 g) were recorded for 8 hr. Pyrexia was induced by the dorsal and ventral subcutaneous administration of two 1 ml quantities of 44% yeast suspension (0.6 ounce cake of Fleischmann's Baker's yeast in 22 ml of 0.9% sodium chloride). The site of injection was then massaged again to stimulate a further increase in body temperature. At 18th hr the rectal temperature was recorded for the second time, using rectal thermometer. This temperature served as the base line temperature from which antipyresis was determined.

*Corresponding Author

The drug was then administered orally as an aqueous suspension made with two drops of Tween 80. Control rats were given saline by the same route. Aspirin and paracetamol were used as standard controls.

For the determination of antipyresis the temperature was noted hourly until 6.5 hr after drug administration.

Ulcerogenic activity : The acute ulcerogenic or gastric mucosal eroding effect of DAPAP was evaluated by modification of the method reported by Hitchens et al. (3). Albino rats of either sex (110-140 g) were starved for 18 hr but given water ad libitum.

A group of 6 rats was kept as control, and to groups of 6 rats each, aspirin DAPAP and paracetamol (doses 150, 160 and 135 mg/kg, respectively) were administered orally. The control groups received 2 ml of 0.5% acacia with 2 drops of Tween 80. Four hr later the animals were sacrificed. The stomach was removed, washed and fixed in 10% formalin. Stomachs were cut along the greater curvature, mounted on flat surface and photographed. They were examined for the presence of eroded or ulcerated areas. Ulcers were scored (4) and ulcer index was thus, calculated.

Analgesic activity : Acetic acid induced writhing test (5) was adopted for evaluation of analgesic activity. Young adult albino mice of either sex (20-25 g) were used. A group of 6 mice was used for control and 6 each for aspirin, DAPAP and paracetamol (aqueous suspensions). The controls were given distilled water with Tween 80. Writhing was induced by an injection of 300 mg/kg of 3% aqueous acetic acid and the number of stretching episodes for next 20 min were recorded.

The percentage protection was calculated using the formula :

$$\text{Percentage protection} = \frac{100 (W_c - W_u)}{W_c}$$

where W_c is the number of writhings in control, and W_u is the number of writhings in treated mice.

RESULTS AND DISCUSSION

Using Student's t-test observations in Table I indicate that DAPAP exhibits significant ($P < 0.01$) antipyretic effect for a duration of 5 hr.

The ulcer index was found to be 4 for aspirin and 0 for DAPAP which shows that DAPAP is devoid of ulcerogenic activity, though ED 50 s were found to be comparable (6).

TABLE I : Comparative study of antipyretic activity of aspirin DAPAP and paracetamol in rats treated with 1 ml of 4% yeast suspensions.

S. No.	Drugs	Dose mg/kg orally	Initial rise	Rectal temperature (Mean±SEM)						
				1 hr	2 hr	2.5 hr	4 hr	5 hr	6 hr	6.5 hr
1.	Control	—	2.5±0.21	2.2±0.1	3.1±0.1	3.2±0.1	3.2±0.2	2.9±0.1	2.5±0.1	2.2±0.2
2.	Aspirin	150	2.4±0.23	0.8±0.1	0.8±0.1	1.8±0.1	1.6±0.2	2.1±0.1	2.6±0.2	3.0±0.1
3.	DAPAP	160	2.5±0.23	1.1±0.2	1.2±0.3	1.2±0.2	1.6±0.2	2.3±0.1	2.8±0.2	3.6±0.1
4.	Paracetamol	125	3.0±0.3	1.0±0.1	1.0±0.2	1.0±0.1	1.8±0.2	2.2±0.1	2.2±0.1	3.4±0.1

n=6 in each group

The percentage protection DAPAP gives against writhing is 3.82 which is negligible when compared to aspirin (Table II).

These studies show that DAPAP can be used as a potent, safe and effective antipyretic drug as it is devoid ulcerogenic action.

TABLE II : Comparative protection offered by aspirin, DAPAP and paracetamol against acute acid induced of writhing in mice.

S. No.	Drugs	Dose mg/kg (oral)	Number of writhings		Percentage protection
			Total	Average	
1.	Control	—	141	23.5	—
2.	Aspirin	165	20	3.33	85.82
3.	DAPAP	175	136	22.6	3.82
4.	Paracetamol	135	22	3.6	84.6

n=6 in each group

REFERENCES

- Poonam S. Studies on interaction between aspirin and paracetamol. Thesis submitted to Nagpur University in partial fulfilment of M. Pharm. Degree 1987.
- Roszkoski AP, Rooks WH, Tomolonis AJ, Miller CM. Anti-inflammatory and analgesic properties of d-2 (6'-Methoxy-2' Nephthyl)-Propionic acid (Naproxen) *J Pharmacol and Expt Therap* 1971; 1 : 114-23.
- Hitchens JT, Goldstein S, Sambuca A, Shemano I. Ulcerogenic effects of non steroidal anti-inflammatory agents in rats. *Pharmacologist* 1967; 330 : 242-3.
- Bonnycastle DD. Agents acting on the alimentary canal. Evaluation of drug activities *Pharmacometrics* 2nd ed. *Academic Press London* 1964; 507-21.
- Witkin LB, Heubner CF, Galdi F, O' Keefe E, Spitaletta P, Plummer AJ. Pharmacology of non narcotic analgesic. *J Pharmacol and Expt Therap* 1961; 133 : 400-408.
- Poonam S, Grover JK. ED50 of DAPAP *Ind J Pharmacol* (to appear).

ACKNOWLEDGEMENTS

The authors wish to thank Mr. S. G. Khas-kedikar for valuable help and University Grants Commission for aiding the project.