LETTER TO THE EDITOR

CARDIAC EFFECTS OF PARACETAMOL

Sir,

The outstanding feature of the widely used analgesic and antipyretic paracetamol is its safety and freedom from side effects in therapeutic doses. However, in cases of poisoning with toxic doses of paracetamol, severe myocardial damage has been reported (2). In therapeutic doses paracetamol is devoid of cardiotoxicity in non-cardiac patients (1). However, after ingestion of paracetamol for 1 to 2 days in therapeutic doses, I personally experienced bradycardia during the afebrile period. In view of the above experience the present pilot study was undertaken.

Ten healthy adult males aged between 24 to 34 years were investigated. The observations were made starting 1 hr after breakfast between 0900 hr to 1100 hr with volunteers comfortably seated in a quiet room. The pulse rate was counted and blood pressure measured thrice at 5 min intervals. Then the volunteers were given 1 g of paracetamol (CROCIN, Crook's Laboratory) or aluminium hydroxide (ALUDROX, John Wyeth) as powder with half a tumbler of water. Blood pressure and pulse rate were recorded thrice, as before, 1 hr after drug administration. During the whole period of study i.e., 30 min before drug administration until the completion of recordings, volunteers were not allowed to have tea, coffee or cigarettes. Studies were conducted using double blind crossover design. For each experiment, the mean of the three control measurements immediately preceeding the treatment and that of three post-drug measurements were calculated and analysed by paired t-test. Adult mongrel dogs (8-11 *kg*) of either sex, anaesthetised with chloralose (70 *mg/kg*, ip) were used for carotid blood pressure recording by the usual method. Lead II of E.C.G. was recorded. Heart rate and blood pressure were recorded before and at 15 min intervals for 2 hr after paracetamol administration (100 *mg/kg*, ip) in normal, bilaterally vagotomised and in atropinized (1 *mg/kg*, iv) animals. The effect of paracetamol on the heart rate and blood pressure responses to adrenaline (5 $\mu g/kg$, iv) was also studied.

Paracetamol was found to produce significant ($P < 0.001$) bradycardia and in all the ten volunteers the diminution in the heart rate ranged from 4 to 14 beats per min with a mean of 8.4. Three volunteers showing relatively higher degree of bradycardia after paracetamol, complained of weakness. The placebo treatment did not produce any significant change in the heart rate. Paracetamol did not produce any significant change in

the diastolic blood pressure. However, there was slight but insignificant reduction in the systolic blood pressure, maximum fall was by 8 mm Hg, the mean being 4.4. The placebo had no significant effect on blood pressure. In anaesthetised dogs paracetamol produced bradycardia in all the 5 dogs studied, the maximum effect being between 40-60 min after drug administration and the effect disappeared in 2 hr. The mean reduction in the heart rate was 16.0 $\pm$ 1.73 per min. There was no significant effect on the blood pressure. The negative chronotropic effect of paracetamol was neither blocked by bilateral vagotomy nor by atropine pretreatment. The positive chronotropic effect of adrenaline was unaffected by paracetamol pretreatment.

The results indicate that the negative chronotropic effect of paracetamol is probably due to the direct action on the myocardium as it is unaffected by vagotomy and cholinergic blockade. The effect is also not due to beta adrenoceptors as the chronotropic effect of adrenaline was unaffected. It therefore, appears that paracetamol has a direct action on the myocardium. The slight diminution in the systolic blood pressure might either be due to bradycardia or due to diminution in myocardial contractility. The unusual weakness in three volunteers after paracetamol might be due to higher degree of bradycardia. This might be the reason why in some countries paracetamol is not used as analgesic and antipyretic. A detailed study of the effects of paracetamol on the heart is warranted.

S.B. ACHARYA
Department oh Pharmacology,
Institute of Medical Sciences
Banaras Hindu University, Varanasi-221 005

REFERENCES

1. Woodbury, M. Dixon and Fingl Edward. Analgesic-Antipyretics, Anti-inflammatory Agents, and drugs employed in the therapy of Gout. In "The Pharmacological Basis of Therapeutics" by Goodman, L.S. and A. Gilman New York, Macmillan Publishing Co., p. 345. 1975.
2. Maclean, D., T.J. Peters, R.A.G. Brown Margaret McCathie, G.F. Baines and P.G.C. Robertson. Treatment of acute paracetamol poisoning. *Lancet,* II : 849. 1968.