The protective effect of sodium meclofenamate in experimental endotoxin shock

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The administration of *E. coli* endotoxin to anaesthetized cats results, within 1-3 min, in a rise in pulmonary artery pressure and in transient decreases in systemic arterial blood pressure and in myocardial contractility. The secondary shock phase is characterized by systemic hypotension, a reduced stroke volume and a severe metabolic acidosis (Parratt, 1973). Only 6% of animals survive longer than 6 h after the intravenous administration of 2 mg/kg of endotoxin. Pretreatment with indomethacin not only abolishes the initial pulmonary hypertension but also delays the onset of the secondary shock phase and increases survival (Parratt & Sturgess, 1974). One possible explanation for these protective effects is inhibition of prostaglandin synthesis and the purpose of the present experiments was to determine the effectiveness of sodium meclofenamate, which is a more active inhibitor of prostaglandin synthetase than indomethacin (Flower, 1974) and which has less marked direct effects on cardiac function.

Sodium meclofenamate (0.5, 2.0 and 5.0 mg/kg, intravenously, when administered up to 6 h before the endotoxin) prevented, or markedly reduced, endotoxin-induced pulmonary hypertension and decreases in pulmonary compliance. In control cats, endotoxin (2 mg/kg, intravenously) increased pulmonary artery pressure from 19 ± 1 mmHg (systolic) and 10 ± 1 mmHg (diastolic) to 41 ± 7 and 27 ± 5 mmHg respectively. The corresponding pulmonary artery pressures in the cats pretreated with sodium meclofenamate (2 mg/kg, 30 min before the endotoxin administration) were, pre-endotoxin 22 ± 2 mmHg (systolic) and 11 ± 1 mmHg (diastolic) and, 3 min after endotoxin, 25 ± 2 and 15 ± 2 mmHg. This dose of sodium meclofenamate also prevented, or delayed, the onset of the shock phase. In control animals the diastolic blood pressure 3 h after endotoxin was a mean of 25 ± 12 mmHg below the mean pre-endotoxin level of 83 ± 5 mmHg. This decrease in diastolic pressure after endotoxin was not observed in the animals pretreated with sodium meclofenamate and 29% of these cats were alive at 6 h (compared with only 6% administered endotoxin alone).

The effects of sodium meclofenamate (2.0 mg/kg) were also examined when administered 30 min after the injection of endotoxin and every 1 h thereafter. This treatment was associated with marked elevations in systemic blood pressure during the shock phase and with increased survival (40% at 6 h).

These experiments support the concept that the release of a prostaglandin (probably $F_{2\alpha}$) mediates the initial pulmonary vasoconstriction that results from endotoxin administration in cats and provides evidence that inhibiting prostaglandin release during the shock phase has beneficial haemodynamic consequences which increase the possibility of survival.

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