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EFFECTS OF MISOPROSTROL ON PENTYLENETETRAZOL-INDUCED SEIZURES IN MICE

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ABSTRACT - The effects of prostaglandin E - analogue misoprostol on the susceptibility to pentilenetetrazol(PTZ) - induced seizures were examined in mice. Misoprostol (200-800 μg/kg), given subcutaneously 45 min before the subconvulsive dose of PTZ (30 mg/kg, i.p) provoked dose-dependent clonic-tonic seizures (30 to 100%) and mortality in mice. At 300 g/kg, s.c., misoprostol pretreatment significantly ($p<0.05$) lowered the onset latency to first convulsion as well as the latency to mortality induced by a convulsive dose of PTZ (60 mg/kg, i.p.). At this dose misoprostol was found to lower the CD_{50} and Ld_{50} values for PTZ by 21% and 36% respectively. The results suggest that prostaglandins are likely to lower the threshold for convulsions.

KEY WORDS: seizures, pentylenetetrazol, misoprostol, mice.

Efeitos de misoprostrol sobre convulsões induzidas por pentilenotetrazol em camundongos

RESUMO - Os efeitos do misoprostrol, um análogo da prostaglandina E, sobre convulsões induzidas por pentilenotetrazol (PTZ) foram estudados em camundongos. Misoprostrol (200-800 μg/Kg) administrado por via subcutânea 45 minutos antes da dose subconvulsiva de PTZ (30 mg/Kg, i.p.) provocou crises tônico-clônicas (30 a 100%) de maneira dose-dependente e mortalidade em camundongos. Na dose de 300 g/Kg, s.c., o pré-tratamento com misoprostrol diminuiu significativamente ($p<0,05$) o período de latência da primeira convulsão bem como a mortalidade induzida por uma dose convulsiva de PTZ (60 mg/Kg, i.p.). Nesta dose o misoprostrol diminuiu 21% e 36% os valores de CD50 e de LD50 do PTZ, respectivamente.

PALAVRAS-CHAVE: convulsões, pentilenotetrazol, misoprostrol, camundongos.

Pentylenetetrazol (PTZ) - induced convulsions in rodents has been considered as an experimental model of epilepsy[9]. Prostaglandins (PGs) are widely used for the termination of second-trimester pregnancies[5,6,13]. The main side effects include nausea, vomiting, diarrhoea, and bronchial spasm[1,4,7,8]. Besides, risks of convulsions have been reported in epileptic women undergoing therapeutic abortion with PGs[2]. Although increases in prostaglandin (PG) release from brain tissue have been demonstrated during both experimentally-induced convulsive seizures as well as in spontaneous seizures[3,14], its significance in induction of seizures is not clear.

Considering the occurrence of convulsions with clinical use of PGs, we have verified in the present study, the acute effects of misoprostol, a prostaglandin E_1 analogue, on PTZ-induced convulsions in mice.

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MATERIAL AND METHODS

Female albino mice weighing 25-30 g were divided into groups of 10 animals each. Three series of experiments were done to verify the effects of misoprostol (Cytotec-Biolab Searle) on PTZ-induced convulsions. In the first series, misoprostol dissolved in normal saline (154 mM NaCl) was administered subcutaneously in graded doses of 200 to 800 µg/kg to each group in a volume of 0.2 ml/mouse. The control animals received an equal volume of normal saline. After 60 minutes, the animals were given a subconvulsive dose of PTZ (30 mg/kg, i.p.) and were observed for signs of CNS excitation such as convulsions and mortality. In the second series of experiments, the effects of misoprostol (300 µg/kg, s.c.) or normal saline pretreatment on the convulsive dose of PTZ (60 mg/kg, i.p.) was studied in relation to onset latency to first convulsion and death. In the third series, the CD_{50} (dose that elicits convulsion in 50% of mice) and LD_{50} (lethal dose to 50% of animals) values of PTZ were established in misoprostol (300 µg/kg, s.c.) pretreated mice and these values were compared to those obtained from saline treated controls.

Values of CD_{50}, LD_{50} of PTZ and the slopes of dose-response curves were established by the method of Litchfieldand Wilcoxon (1949). The student t-test was used to assess the significance between groups; $p<0.05$ was taken as the level of significance.

RESULTS

The subconvulsive dose of PTZ (30 mg/kg) did not provoke convulsions or deaths in control animals while in mice pretreated with misoprostol, convulsions and deaths appeared in a dose dependent manner (Fig 1). The convulsive dose of PTZ (60 mg/kg) however lead to convulsions in both controls as in misoprostol (300 µg/kg) pretreated mice. Misoprostol pretreatment significantly ($p<0.05$) lowered the onset latency to first convulsion (controls 96±12 sec; misoprostol 85±7 sec) and also the latency to death (controls 740±98 sec; misoprostol 373±100 sec). Table 1 shows the effects of misoprostol pretreatment on the convulsive action of PTZ. Misoprostol (300 µg/kg, s.c.) significantly ($p<0.05$) reduced the convulsive ED_{50} as well as the LD_{50} of PTZ.

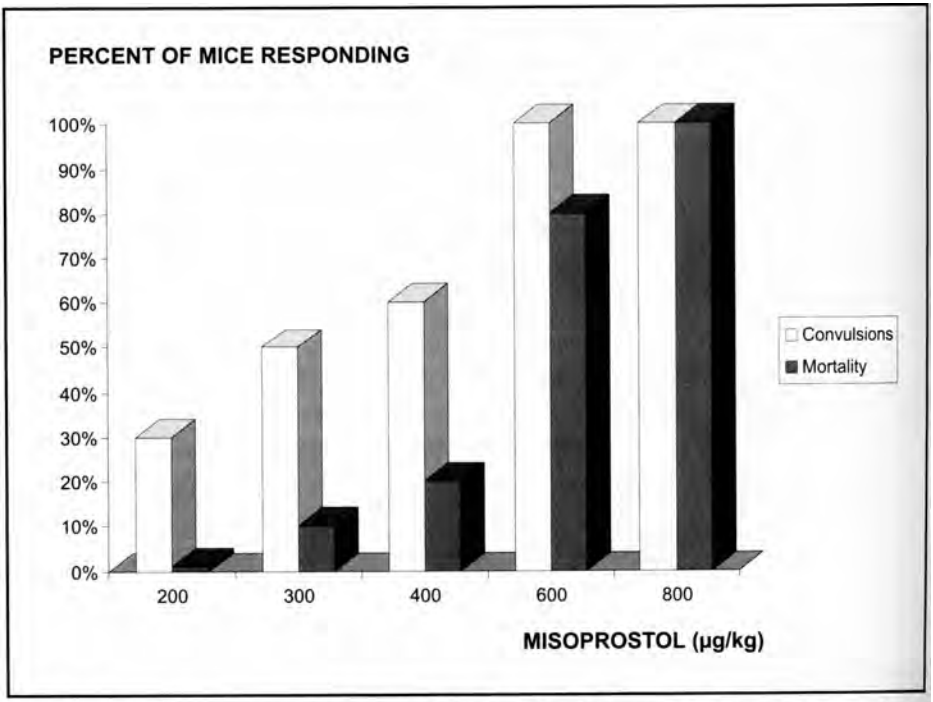

Fig 1. Convulsions and mortality after a subconvulsive dose of PTZ (30 mg/kg) in misoprostol pretreated mice.

Table 1. Effect of misoprostol on PTZ-induced convulsion and death in mice.

Pretreatment	CD_{50} (mg/kg)	Slope	Ld_{50} (mg/kg)	Slope
Normal saline	38 (27.1-53.2)	1.54 (0.93-2.54)	55 (47.0-64.4)	1.12 (0.74-1.70)
Misoprostol	28 (24.1-32.5)	1.27 (1.07-1.50)	35 (29.9-41.0)	1.10 (0.73-1.67)

Mice were pretreated with either normal saline or misoprostol (300 μg/kg, s.c) half an hour before i.p. injection of PTZ in graded doses (10-100 mg/kg).The 95% confidence interval is given in parenthesis.

DISCUSSION

Reports so far appeared in literature on the role of PGs in induction of seizures by PTZ are conflicting, most studies have used prostaglandin-synthetase inhibitors to elicit the role of prostaglandins. In some studies, indomethacin was found to reduce brain prostaglandin levels and onset latency to seizure induced in the mouse[4,11] while, in few other studies, mefenamic acid, meclofenamic acid, ibuprofen and paracetamol were found to delay the onset of PTZ-induced convulsions[12] suggesting to these investigators that PGs play a stimulatory role in convulsion induction.

In the present study, the effects of the both subconvulsive and convulsive doses of PTZ were modified by the prostaglandin E_1 analogue, misoprostol. Misoprostol hastened the onset latency to first convulsion and also effectively reduced the convulsive ED_{50} of PTZ which suggest that PGs lower the threshold for seizure induction.

However, it is difficult to speculate the exact role of PGs in seizure induction. The central excitatory processes are mediated via neurohumors like catecholamines and acetylcholine. Involvement of cholinergic mechanisms in PTZ-induced convulsions has been suggested[10]. A rise in the levels of central cathecolamines seems to be unfavorable to the production of experimental convulsions. PGs may alter the levels of these neurohumors and potentiate the action of PTZ.

The clinical significance of the present study is that, prostaglandins should be used cautiously to epileptic women undergoing therapeutic abortion.

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