Date :

Title : FRUCTOSE DI PHOSPHATE: ANALEPTIC FOR A BARBITURATE

Authors : A. K. Markov, M.D., N. Oglethorpe, M.S., M. D. Turner, Ph.D., D. B. Young, Ph.D., J. W. Jones, M.D., and H. K. Hellems, M.D.

Affiliation: Departments of Medicine, Surgery, and Physiology, University of Mississippi Medical Center, Jackson, Mississippi 39216

Introduction. Experimentally it has been demonstrated that barbiturates when given in anesthetic concentrations cause a significant decline in carbohydrate utilization by the brain.[1] The mechanism responsible for inducing this partial metabolic block in the Embden-Meyerhof pathway has been attributed to inactivation of phosphofructokinase(PFK) by barbiturates.[2] In myocardial infarction, and in hemorrhagic and endotoxic shock, glycolysis is severely depressed secondary to inactivation of PFK by acidosis.[3] Intravenous administration of fructose 1,6 diphosphate (FDP) appears to restore the depressed activity of glycolysis in these conditions, by intervening in the pathway both as a metabolic regulator and a high energy substrate as evidenced by: (1)In acute myocardial infarction FDP administration vastly improves the myocardial performance.[4] (2)In irreversible hemorrhagic shock studies all FDP-treated dogs survived, while all controls died.[5] (3)In dogs subjected to lethal doses of endotoxin, FDP reduced mortality to 10%.[6] In these studies it was noted that the dogs receiving FDP (n=104) required twice as much anesthetic to be maintained in a state of surgical anesthesia as did the controls (n=103). Hence, the present study was undertaken to evaluate more objectively the analeptic effect of intra-arterial administration of FDP on Surital (thiamylal) anesthesia in dogs.

Methods. In this paired study 10 dogs were anesthetized with Surital 35mg/kg IV. Within 10 minutes after induction of anesthesia, a #7 Sones catheter was placed in a common carotid artery via the femoral artery under fluoroscopic guidance. Injection of contrast media verified that the position of the catheter did not obstruct the vessel, and portions of the brain were opacified transiently. Immediately following the contrast media injection the infusion of FDP or glucose was initiated (9-13 min after induction of anesthesia). The FDP was prepared as a 5% solution and infused at a constant rate of 1.91 ml/min (97.5 mg/min) into a main carotid artery. The controls received equal amounts of 5% dextrose via the same route. The analeptic effect of FDP on signs, stages and depth of anesthesia was evaluated by determining the time required for reappearance of eyelid reflex, opening of eyes, deglutition, response to pain, lifting of the head, sitting, and when the animal was able to walk. These data were compared with like data from the group that received 5% dextrose.

Results. The time required for return of observable eyelid reflex after beginning the infusion into the carotid artery was 3.70±0.67 min in the FDP-treated dogs, while for the controls the time was 70.00±25 min(±SDM). The time required to regain walking ability was significantly shorter (76.6±16 min) in the FDP treated dogs than in the dextrose controls (295.00±24.49 min)($p<0.001$). The table below summarizes the results.

Time in Minutes after Beginning of Infusion

Dog No.	Eyes Open	Response To Pain	Lifts Head	Able To Sit	Able To Walk
FDP					
1	7	17	28	48	60
2	14	19	33	47	70
3	5	10	14	35	50
4	12	18	19	52	95
5	4	15	20	40	82
Glucose					
1	80	120	170	300	310
2	75	130	135	225	300
3	105	160	190	310	330
4	54	125	165	215	280
5	40	100	120	310	265

Conclusions. Intra-carotid administration of FDP to animals subjected to thiamylal anesthesia greatly reduces the time required for the animal to regain consciousness and be able to walk. The same analeptic effect, but to a much lesser degree, is observed when FDP is administered systemically. Since FDP has been shown to have profound antishock activity in experimental animals and in man, that phenomenon - taken with the effects of FDP observed in this study - indicates that FDP may have clinical potential in the treatment of barbiturate overdose.

References.

1. Harp Jr, Siesjö BK: Effects of anaesthesia on cerebral metabolism, A Basis and Practice of Neuroanaesthesia. Edited by Gordon E. Amsterdam, Exerpta Medica, pp. 83-112, 1975
2. Chapman AG, Nordström C-H, Siesjö BK: Influence of phenobarbital anesthesia on carbohydrate and amino acid metabolism in rat brain. Anesthesiology 48:175-182,1978
3. Mansour TE: Studies on heart phosphofructokinase: purification, inhibition and activation. J Biol Chem 238:2285-2292,1963
4. Markov AK, Oglethorpe N, Blake TM, et al: Hemodynamic, electrocardiographic and metabolic effects of fructose diphosphate on acute myocardial ischemia. Am Heart J, in press
5. Markov AK, Oglethorpe N, Young DB, et al: Fructose di phosphate: An agent for successful treatment of irreversible hemorrhagic shock. Clin Res 27:440A, 1979
6. Markov A, Turner D, Oglethorpe N, et al: Fructose 1-6 diphosphate: An agent for treatment of experimental endotoxic shock. Clin Res 27:674A, 1979