

Ornithine Phenylacetate (OP) prevents neurophysiological abnormalities in an experimental model of hepatic encephalopathy

Liver Unit. Hospital Universitari Vall d'Hebron. Barcelona. Spain

Marc Orià, Jordi Romero-Giménez, Núria Ragner, Jose Antonio Arranz, Juan Córdoba.

Introduction: Ornithine phenylacetate (OP) is a new compound that decreases blood ammonia and has shown to prevent brain edema in experimental models. The assessment of motor evoked potentials (MEP) after the infusion of blood in the duodenum of rats with portocaval anastomosis (PCA) is an experimental correlate of hepatic encephalopathy precipitated by variceal bleeding.

Aim: Study the efficacy of OP in experimental HE precipitated by blood in the gastrointestinal tract in rats with PCA.

Material and methods: PCA rats were pretreated with OP (0.6 g/kg/day) or saline intraperitoneally (n=8 per group) prior to the infusion of blood (bolus of 4 ml every hour over 4 hours). Motor evoked potentials (MEP) were elicited after central and peripheral stimulation without anesthesia using subcutaneous electrodes located in the skull, sciatic nerve and tibialis anterior muscle. Brain microdialysis was performed over 24 hours and nitrogenous compounds were determined by HPLC.

Results: The infusion of blood induced an increase in the latency (\uparrow) and a decrease in the amplitude (\downarrow) of MEP (table). Pretreatment with OP attenuated MEP abnormalities and decreased the rise in plasma ammonia.

Brain microdialysis showed after the infusion of blood a marked rise in glutamate and glutamine (approx 200%) and a drop in isoleucine (approx 50%). OP attenuated these abnormalities (glutamate/glutamine by 20% and isoleucine by 50%).

Time postGIB	Control (saline)			Ornithine-Phenylacetate		
	Latency (%)	Amplitude (%)	Ammonia (mM)	Latency (%)	Amplitude (%)	Ammonia (mM)
2 hours	104 \pm 3	90 \pm 3 \downarrow	176 \pm 46	100 \pm 4	103 \pm 8*	109 \pm 41*
4 hours	109 \pm 5 \uparrow	83 \pm 6 \downarrow	244 \pm 120 \uparrow	102 \pm 4*	101 \pm 7*	174 \pm 72*
6 hours	112 \pm 7 \uparrow	79 \pm 10 \downarrow	287 \pm 88 \uparrow	103 \pm 6*	99 \pm 9*	162 \pm 84*
8 hours	112 \pm 8 \uparrow	91 \pm 10 \downarrow	273 \pm 93 \uparrow	101 \pm 6*	104 \pm 10*	158 \pm 79*
24 hours	104 \pm 4	106 \pm 7	171 \pm 82	97 \pm 4	118 \pm 10*	118 \pm 44

%= change compared to time=0 $\uparrow\downarrow$ p<0.05 vs baseline *p<0.05 vs control

Conclusions: Ornithine phenylacetate prevents impairment of neurophysiologic signal transduction (a functional measure of HE) precipitated by blood in the gastrointestinal tract. These effects appear to be mediated by preventing hyperammonemia that follows digestion of gastrointestinal blood. Ornithine phenylacetate represents a novel treatment that could be effective to prevent HE precipitated by variceal bleeding.