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THE EFFECT OF PROSTAGLANDIN E1 ON THE COURSE OF DECOMPRESSION S--ETC(U)
OCT 77 J M YOUNG, J M HALLENBECK, R M FINE

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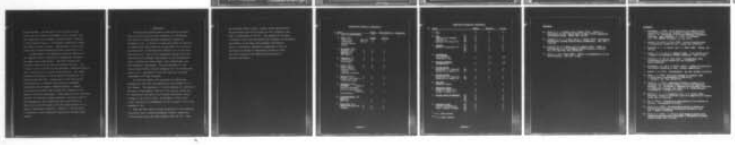

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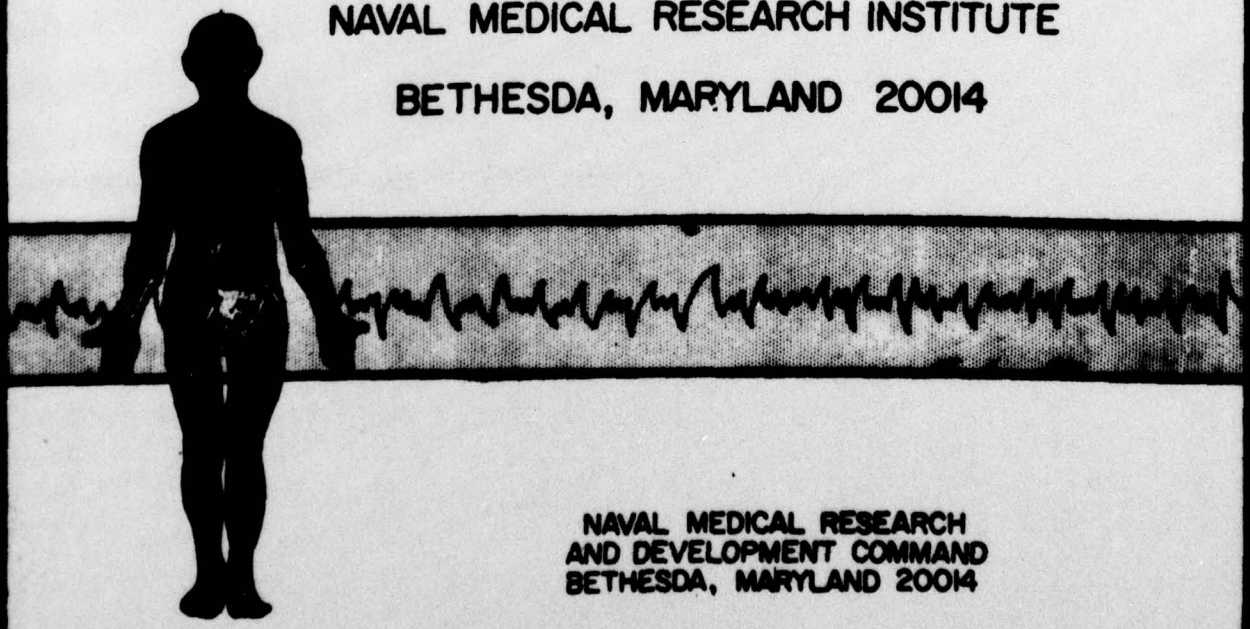
THE EFFECT OF PROSTAGLANDIN E_1 ON THE COURSE OF DECOMPRESSION SICKNESS IN DOGS

J. M. YOUNG, J. M. HALLENBECK and R. M. FINE

Hyperbaric Medicine and Physiology Department

NAVAL MEDICAL RESEARCH INSTITUTE

BETHESDA, MARYLAND 20014



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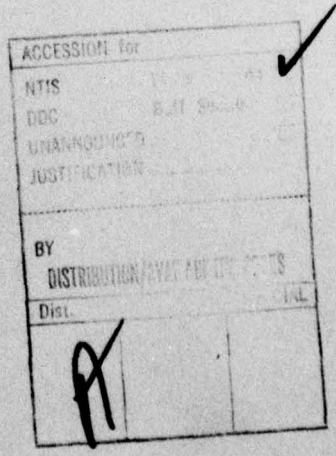

THE EFFECT OF PROSTAGLANDIN E_1 ON THE COURSE OF DECOMPRESSION SICKNESS IN DOGS

by

J.M. Young, J.M. Hallenbeck and R.M. Fine

Naval Medical Research Institute
Hyperbaric Medicine and Physiology Department
Neurophysiology Division
Bethesda, Maryland 20014

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ABSTRACT

A 'double-dive' technique was used to produce neurological symptoms of decompression sickness in four air-breathing dogs. The neurological deficit was quantitatively scored and then an intravenous infusion of Prostaglandin E_1 (PGE_1) was given at a dose rate of 10 µg/kg/minute. The results were compared to those previously obtained when using a similar technique to investigate other therapeutic agents in the treatment of decompression sickness.

There was no evidence of any improvement in the clinical condition of the dogs treated with PGE_1 and rapid deterioration and death occurred in 3 out of 4 animals. This may indicate that PGE_1 has an actively deleterious effect on dogs with neurologic manifestations due to severe decompression sickness.

INTRODUCTION

The aetiology of decompression sickness (DS) is most probably due to the production of microbubbles in the blood stream or tissues. These bubbles grow in size as pressure is reduced and those in the circulation become coated with an aggregation of plasma proteins, lipids, and platelets (13). The clinical signs of DS are presumably caused by the bubble and aggregate mass, eventually interrupting tissue perfusion with resultant localized tissue hypoxia and cessation of function of the affected tissue.

Much attention has been given over the past decade to pharmacological agents which theoretically could alter the incidence of DS or alleviate the clinical course of the disease. Most of the agents used have been known to cause an effect on the coagulability of blood and platelet adhesiveness or the formation of lipid emboli. Agents studied have included heparin (1, 12), aspirin (2, 9), dicumarol (9), methylsiloxone (10), dipyridamole (9, 14), and rheomacrodex (4, 15). The results of these experiments have often been equivocal and sometimes contradictory, with apparent species variations explaining differences in effectiveness of an agent and also differences in experimental techniques used by researchers contributing to

contrasting results.

Recent work demonstrates that a common factor among the agents used is that they are all interrelated with actions of various prostaglandins (PG's) and with cyclic adenosine monophosphate (CAMP) (7). The current knowledge of the exact actions of PG's does not allow a reasoned approach to the question of possible effectiveness of PG's in the treatment of decompression sickness. However, prostaglandin E_1 (PGE_1) has been shown to have effects which could be beneficial in the treatment of DS. PGE_1 causes dilatation of the pulmonary circulation (8) and reduces peripheral vascular resistance with dilatation of muscle and skin vascular beds (17); it inhibits the aggregation of platelets caused by a variety of substances (3) and reduces the rise in peripheral vascular resistance caused by endotoxin administration (16). All of these effects could theoretically reduce the risk of embolization and in combination with conventional recompression and supportive therapy reduce the severity of clinical DS.

METHODS

Six mongrel dogs were exposed to increased atmospheric pressure in a 'double-dive' profile. The animals had been splenectomized at least 3 weeks before the experiment and were fully recovered and in good health. The weights of the dogs were between 9.4 kg and 13.0 kg, with a mean (±SD) of

11.4 (±1.4). Quantitative neurological examinations and hematocrit determinations were performed pre-exposure, post-exposure, and at intervals thereafter. Following the pressure exposure and after the appearance of symptoms of DS, an infusion of PGE_1 was given and the progress of the signs of DS were observed.

Pressure exposure

Dogs were compressed in a chamber (Bethlehem) to a simulated depth of 220 ft (67 m) at the rate of 75 ft/min (23 m/min). Time at pressure was 40 minutes, counting from leaving normal atmospheric pressure to leaving maximum pressure. Decrease of pressure to 1 ATA was continuous at the rate of 60 ft/min (18 m/min). Following return to normal pressure the dogs were closely observed for signs of DS which usually occurred within 5 minutes. Immediately after definite signs were seen, the dogs were recompressed to 70 ft (21 m) in 1 minute, held at that pressure for a minute, returned to 30 feet for a further minute and then a variable decompression schedule was started to normal pressure which aimed at a rate of 6 ft/min (1.8 m/min) but depended on the state of the animal. If symptoms of paralysis were observed at anytime, the decompression was halted for 1 minute and then resumed at a rate which would preserve the paralysis but would prevent development of cardiorespiratory collapse.

Neurological examination

A neurological examination was performed before the pressure exposure, immediately after the exposure, and at approximately 1/2-hour intervals thereafter. These examinations were quantitatively scored according to a method developed at the Naval Medical Research Institute by Hallenbeck and Elliott (6); the scoring used is attached as Appendix I.

Infusion of PGE_1

A supply of crystalline Prostaglandin E_1 was obtained (Upjohn Company, Lot #11918-FHL-143) and stored at $-4^{\circ}C$. Shortly before the experimental series were started, the crystalline PGE_1 was dissolved in 95% ethanol to give a concentration of 10 mg/ml. Aliquots of the solution, each containing 1 milliliter, were stored at $-20^{\circ}C$ in capped plastic tubes. On the morning of the experiment an aliquot of the solution was diluted with normal saline to give the desired concentration of PGE_1. Administration of PGE_1 was by continuous intravenous infusion to take account of the destruction of PGE_1 which occurs on its passage through lung tissue. This degradation is thought to be related to the presence of dehydrogenase in the lungs and is of the order of 90% on each passage (5). The dose of PGE_1 infused was 10 µg/kg/min (11), giving an effective arterial dose of about 1 µg/kg/min. Infusion was by a variable speed rotary pump (Holter, type RD 074) via a catheter placed in the right saphenous vein.

Fluid replacement

The dogs' pre-exposure plasma volume was calculated as 5% of its pre-exposure weight; i.e., a 10 kg dog was assumed to have a 500 ml plasma volume.

Duplicate determinations of hematocrit (Hct) were made pre-exposure (control), post-exposure and at 1/2-hour intervals. The fluid replacement requirement in milliliters was calculated as:

$$\frac{Hct_{sample} - Hct_{control}}{Hct_{control}} \times kg_{pre\text{-}exposure} \times 50$$

The volume required was administered by intravenous infusion of normal saline via a catheter placed in the left saphenous vein.

RESULTS

Two animals (experiments III and V) developed severe DS which progressed from bilateral hindquarter paresis to quadriparesis and then to respiratory paralysis. Their symptoms did not respond to further recompression therapy and the animals died while still at increased pressure in the chamber.

In experiment I, the PGE_1 infusion was started 24 minutes after the animal had left the chamber. The post-dive quantitative neurological score (QNS) was 36 (Table I) with paresis of all limbs but a more pronounced weakness in

the hindlegs than in the forelegs. At no time during the decompression or before the infusion commenced was any sign of respiratory distress seen. After 14 minutes infusion of PGE_1, nasal secretions were noticed and respiratory distress became evident. Fifty-three minutes after surfacing and leaving the chamber and 29 minutes after starting the PGE_1 infusion, rapid deterioration occurred with the QNS increasing to 46, manifested by copious secretions from mouth and nose, extreme respiratory distress and eventually, cessation of respiration.

In experiment II, the immediate post-dive QNS was 19. A paresis of the hindquarter was evident and the animal appeared to be in a stable condition. The infusion of PGE_1 was started 14 minutes after the animal had left the chamber. Over the next hour there was a slight improvement in the animal's condition with a return of the patellar reflexes and the strength of the left hind limb. No further improvement occurred during the second hour so the infusion was stopped. At 24 hours the dog's condition had worsened with QNS 15, paralysis of the right hind limb, a return of the paresis of the left hind limb, and the animal was then sacrificed.

In experiment IV, the animal had paralysis of all 4 limbs. The PGE_1 infusion was started 6 minutes after reaching surface and while the neurological examination

was proceeding. The QNS was 45 with cranial nerves intact but with severe involvement of the cervical cord. The respiratory rate suddenly increased after 4 minutes of PGE_1 infusion and at 4 1/2-minutes respiration ceased and cardiac arrest occurred. Resuscitation efforts were unavailing although intermittent heart beats were felt.

In experiment VI the immediate post-dive QNS was 32, the symptoms mainly consisting of hindquarter paralysis and right front limb paresis. The PGE_1 infusion was started 24 minutes after the dog finished the dive. The increase in Hct from 45% to 49% indicated a hemoconcentration with a fluid loss of at least 50 milliliters. The animal was given an infusion of 50 ml saline intravenously, 28 minutes after the dive. Pulse rate at this time was 80 beats/minute but 3 minutes later the pulse weakened noticeably and decreased to 68/beats/minute. Another 50 ml saline was given and a repeat Hct remained at 49% despite the fluid replacement. Forty minutes after finishing the dive (16 minutes of PGE_1 infusion), pulse was noted at 64 beats/minute, and respirations were also 64/minute. QNS at this time had risen to 49 with quadriparesis but no sign of respiratory paralysis. However, 5 minutes later (21 minutes of PGE_1 infusion) respirations and heart beat ceased.

DISCUSSION

The same dive profile used in this project had been used in previous work in this laboratory to investigate the effects of other possible therapeutic agents for treatment of DS. A series of 4 dogs were given an infusion of rheomacrodex which resulted in mean QNS's of pre-dive-0, post-dive-16.5, 30 minutes after therapy-4.5, and 24 hours post-dive-19.0. None of the threapeutic agents tried were associated with permanent improvement in the neurological state, although the series above, with rheomacrodex, did show temporary improvement. The one experiment in the current series which could be compared with the rheomacrodex series (i.e., experiment II) did not show any sustained improvement with PGE_1 infusion.

In previous series, the occurrence of respiratory symptoms was rare once the animals had been brought out of the chamber. The appearance of florid symptoms of respiratory distress in experiments I and IV of the current series may be significant and point to an actively deleterious effect of PGE_1 on the course of DS. An infusion of PGE_1 alone cannot therefore be recommended for the treatment of existing symptoms of DS.

PGE_1 has been shown to cause dilatation of the pulmonary circulation and to reduce peripheral vascular resistance by dilatating muscle and skin vascular beds (8, 17). This

may decrease venous return, cardiac output and arterial blood pressure and could account for the collapse of the dogs in experiments IV and VI. The opening of the micro-circulation could also facilitate the transport of peripheral gas bubbles to the heart and pulmonary circulation. Onset of respiratory symptoms in experiment I and the respiratory collapse in experiments IV and VI could have been caused by the sudden central influx of multiple gas emboli.

QUANTITATIVE NEUROLOGIC EXAMINATION

I. Brain		Normal	Semi Conscious	Unconscious
A. Level of consciousness		0	1	2
B. Optic (II) -		Normal	Involved	
visual field	Right (R)	0	2	
(funduscopic optional and not scored)	Left (L)	0	2	
C. Oculomotor (III)				
Trochlear (IV)	R	0	2	
Abducens (VI)	L	0	2	
EOM, pupils				
D. Trigeminal (V)	R	0	2	
corneal reflex	L	0	2	
jaw strength				
E. Facial (VIII)	R	0	2	
facial symmetry	L	0	2	
palpable fissure equality				
clenching of eyelids				
F. Auditory (VIII) -	R	0	2	
blink to loud noise or attend soft noise	L	0	2	
G. Vestibular (VIII) -		0	2	
nystagmus - R and/or L				
forced eye deviation				
head tilt and rotation - R and/or L		0	2	
pleurothotonus				
H. Glossopharyngeal (IX)				
vagus (X)				
gag reflex		0	2	
I. Hypoglossal (XII)				
tongue protrusion and movement	R	0	2	
	L	0	2	

QUANTITATIVE NEUROLOGIC EXAMINATION

II. Spinal		Normal	Moderate	Severe
A. Gait		0	0	2
B. Tone	RF	0	1	2
hypertonic (1) extensor	LF	0	1	2
rigidity (2)	RH	0	1	2
hypotonic (2) flaccid (2)	LH	0	1	2
C. Weakness	RF	0	1	2
paretic (1) paralytic (2)	LF	0	1	2
	RH	0	1	2
	LH	0	1	2
D. Coordination				
jerky movements				
trembling at rest		0	1*	2**
E. Abnormal movements				
choreiform etc.		0	1*	2**
F. Triceps reflex				
hyperactive (1) clonus (2)	RF	0	1	2
hypoactive (1) absent (2)	LF	0	1	2
G. Patellar reflex				
hyperactive (1) clonus (2)	RH	0	1	2
hypoactive (1) absent (2)	LH	0	1	2
H. Anal wink				
present or absent		0		2
I. Panniculus reflex				
present or absent on R		0		2
present or absent on L		0		2
J. Placing reflex blindfolded	RF	0		2
	LF	0		2
	RH	0		2
	LH	0		2
K. Response to pain	RF	0		2
reaction to pinching on	LF	0		2
limbs - present or absent	RH	0		2
	LH	0		2

* 1 or 2 limbs involved

** 3 or 4 limbs involved

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