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Effects of nicotinic acid on plasma volume loss of experimental dysbarism

J. G. HILTON and C. H. WELLS

Department of Pharmacology and Toxicology, and Physiology and Biophysics, The University of Texas Medical Branch and Shriners Burns Institute, Galveston, TX 77550

Hilton, J. G., and C. H. Wells. 1976. Effects of nicotinic acid on plasma volume loss of experimental dysbarism. Undersea Biomed. Res. 3(2):157-161.–Two groups of dogs anesthetized with sodium pentobarbital were subjected to compression of 60 psig for 60 min and decompressed at the rate of 10 psi/min without staging. Plasma volume was measured in each group by I^{131}-tagged albumin dilution technique prior to compression, 10 min and 60 min after decompression. One group of animals received no other treatment and the other group received 15 mg/kg of body weight of nicotinic acid by intravenous injection immediately prior to compression and an additional 7.5 mg/kg of body weight of nicotinic acid 30 min after decompression. Both the untreated and the nicotinic acid-treated animals lost significant plasma volume at both the 10- and 60-min postdecompression measurements. Nicotinic acid-treated animals lost significantly less plasma.

dysbarism
vasoactive substances
nicotinic acid
prostaglandin
plasma-volume loss

The development of significant reductions in plasma volume in experimental or accidental dysbarism has been documented. Losses of 25 to 40% have been observed in dysbaric experimental animals (Cockett and Nakamura 1964; Jacobs and Stewart 1942). Hemoconcentration, which may also be considered as indirect evidence of plasma-volume loss, has been observed by numerous investigators in experimental dysbarism (Carson 1942; Cockett, Nakamura, and Franks 1965). Brunner has reported plasma-volume losses of 20% or more in cases of human dysbarism (Brunner, Frick, and Bühlmann 1964).

The role of vasoactive substances in the development of this plasma loss has not been thoroughly explored. Chryssanthou, Kalberer, Kooperstein, and Antapol (1971) suggested that bradykinin is involved in the pathogenesis of dysbarism. The effects of this agent on vascular permeability are well-established. It is reasonable to wonder if the mechanisms responsible for dysbaric plasma-volume losses do not also involve other vasoactive substances. In experimental inflammation the initial phases of the fluid extravasation appear to result from the effects of kinins, histamine, and serotonin (DiRosa, Giroud, and Willoughby 1971a; DiRosa, Papadimitciou, and Willoughby 1971b). Prostaglandins appear important in later stages of the plasma extravasation.

Recent studies from our laboratory have shown that indomethacin, a prostaglandin synthetase inhibitor, will significantly reduce the plasma-volume loss in dysbaric dogs (Wells, Hilton, and Rosenbaum *in press*). It has also been demonstrated that nicotinic acid will

markedly reduce the plasma-volume loss in dogs following thermal trauma (Hilton and Wells 1975, 1976). Since the postulated mechanism for this effect of nicotinic acid is based upon the inhibition of release of free fatty acid precursors for the formation of prostaglandins, a mechanism potentially applicable to dysbarism as well as to burn, it was considered important to determine whether or not this drug would significantly alter the plasma-volume loss in experimental dysbarism.

METHODS

Two groups of mongrel, sodium pentobarbital-anesthetized dogs, ranging from 8 to 16 kg of body weight, were used for this study. One femoral artery and one femoral vein of each animal was catheterized with polyethylene tubing (Clay Adams PE-220) for sample collection and I^{131}-tagged albumin injection, respectively. Three plasma-volume determinations were carried out on each animal: one before compression, one beginning 10 min after decompression, and one beginning 60 min after decompression. For the first determination, 0.9 μCi of I^{131}-tagged human serum albumin was injected into the vein and arterial blood samples were collected at 10, 20, 30, and 40 min after injection. The plasma volume at the time of injection was determined by standard tag-dilution principles employing retrograde extrapolation of tag concentration to the time of injection. Subsequent determinations were similarly conducted using doses of I^{131}-tagged albumin of 1.8 and 2.7 μCi for the second and third determinations, respectively.

All animals were placed in the Bethlehem Hyperbaric Chamber after completion of the first plasma-volume determination and compressed to 5 ATA in a mixture of 5% oxygen, 95% nitrogen. After 60 min at this pressure, the animals were decompressed. Compression and decompression were conducted at 10 psi/min without staging. The chamber was flushed at a rate of 10 liters/min throughout the compression period.

Animals of the experimental group (n=7) received 15 mg/kg of nicotinic acid intravenously 5 min before compression and 7.5 mg/kg of nicotinic acid 30 min after decompression. The control group (n=7) received no drug.

RESULTS

The mean plasma volume in the untreated animals prior to compression was 55 ± 4 ml/kg body weight; that of the animals receiving nicotinic acid was 56 ± 1 ml/kg body weight. Plasma volumes determined 10 min after decompression were found to be 51 ± 2 ml/kg of body weight for the nicotinic acid-treated animals and 44 ± 2 ml for the animals in the untreated group. One hour after decompression the plasma volumes were 44 ± 2 ml/kg body weight for the nicotinic acid-pretreated group of animals and 31 ± 2 ml/kg body weight for the untreated group of animals.

Prior to compression, differences between the plasma volumes of the two groups of animals were slight and not statistically significant. After decompression, the mean plasma volume of each group was significantly ($P < .01$) less than corresponding precompression values.

The decrease in plasma volume in ml/kg observed in the untreated and nicotinic acid-pretreated animals is shown in Fig. 1. The loss in the treated animals was significantly ($P < .01$) less than that of the untreated animals 10 min after decompression. One hour after decompression the nicotinic acid-pretreated animals' average plasma-volume loss was 12 ± 2 ml/kg body weight, which was substantially less than that of the untreated animals (23.5 ± 3.5 ml/kg). This difference was also statistically significant ($P < .01$).

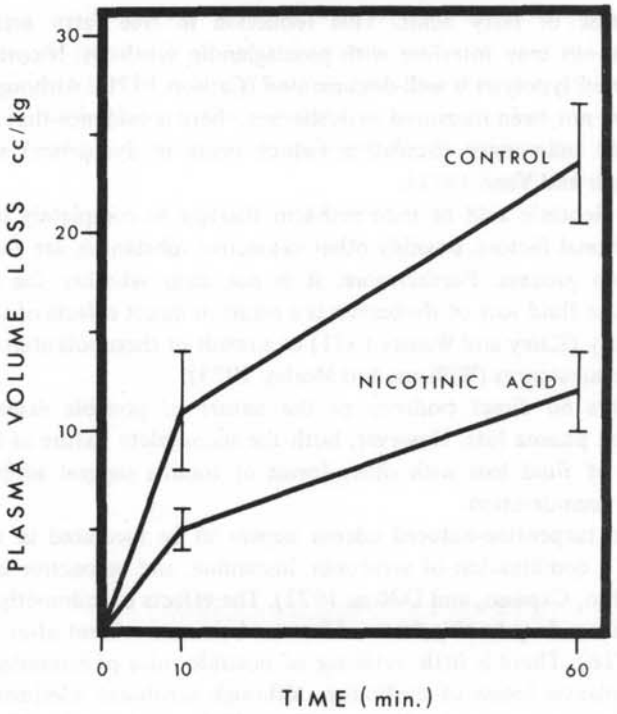

Fig. 1. Plasma-volume loss in the dog following rapid decompression. Ordinates: plasma-volume loss in cc/kg; abscissae: time postdecompression. Control–untreated animals ($n = 7$). Nicotinic acid-treated animals ($n = 7$). Small bars represent standard error.

DISCUSSION

Our studies reveal a loss in plasma volume after decompression, as determined by serial radioactively tagged serum albumin-dilution techniques, that was substantially less in nicotinic acid-pretreated animals than in animals receiving no drug treatment. All experimental animals were subjected to identical compression and decompression schedules.

Comparison of the effectiveness of nicotinic acid in these studies and indomethacin in the results reported by Wells et al. *in press* in reducing the plasma-volume loss following rapid decompression shows that each of these agents produces approximately the same amount of blockade of loss. Except for the choice of pharmacologic agents, the experimental protocols of both this and the indomethacin study cited above were virtually identical. At the end of the 60-min observation period, the average plasma loss was 12 ± 2 ml/kg body weight in the nicotinic acid-treated animals and 9 ± 2 ml/kg body weight in those animals treated with indomethacin. The differences between these two groups of animals is not statistically significant ($P < .3$).

The mechanism by which nicotinic acid prevents the postdecompression loss of plasma volume is unknown. However, the effectiveness of both this agent and indomethacin suggests that a block of prostaglandin synthesis is involved in this reduction of plasma loss. Hilton and Wells (1975, 1976) in their report of the nicotinic acid-induced reduction of plasma loss in thermally injured animals postulated that the mechanism might involve blockade of

stress-induced release of fatty acids. This reduction in free fatty acid precursors for prostaglandin synthesis may interfere with prostaglandin synthesis. Nicotinic acid suppression of stress-induced lypolysis is well-documented (Carlson 1971). Although blood levels of prostaglandins have not been measured in dysbarism, there is evidence that either bubbles or microemboli in the pulmonary circulation (which occur in dysbarism) will cause prostaglandin release (Piper and Vane 1971).

The failure of nicotinic acid or indomethacin therapy to completely block plasma loss suggests that additional factors, possibly other vasoactive substances, are also involved in the plasma-extravasation process. Furthermore, it is not clear whether the apparent role of prostaglandins in the fluid loss of dysbarism is a result of direct effects of these agents upon vascular permeability (Kaley and Weiner 1971) or a result of their potentiation of the effects of other vasoactive substances (Williams and Morley 1973).

This study offers no direct evidence of the nature of possible vasoactive substances involved in dysbaric plasma loss. However, both the incomplete nature of the blockade and results of studies of fluid loss with other forms of trauma suggest additional vasoactive substances deserve consideration.

Carrageenan-and turpentine-induced edema appear to be mediated in the first 2 hours after challenge by a combination of serotonin, histamine, and vasoactive kinins (DiRosa et al. 1971a; Sorrentino, Capasso, and DiRosa 1972). The effects of indomethacin blockade on edema formation secondary to this form of trauma becomes evident after the second hour (DiRosa et al. 1971b). There is little evidence of possible roles of histamine or serotonin as mediators of the plasma losses of dysbarism, although serotonin administration has been shown to increase the severity of the disorder (Clark, Philp, and Gowdey 1969).

Chryssanthou and collaborators (1971) have accumulated substantial evidence that bradykinin is involved in the pathogenesis of dysbarism. While there is little evidence that this substance plays a role in the genesis of dysbaric plasma losses, evidence of its presence in dysbarism and its well-known vascular properties indicate that it is likely to be involved in some aspects of the fluid-loss mechanism.

This study was designed to investigate one of several possible mechanisms of plasma loss in dysbarism. The effectiveness of nicotinic acid in this study and indomethacin in previous studies in reducing these losses suggests that prostaglandin synthesis may play a substantial role in this fluid-loss mechanism. The possible therapeutic implications of this finding remain to be demonstrated. These studies utilized pretreatment before decompression. No effort was made to assess the efficacy of this agent on plasma loss of dysbarism when given after the animal was subjected to decompression stress. Prior studies of the prostaglandin synthetase-inhibiting substances failed to establish the usefulness of these agents in dysbarism (Williams, Lyons, Bridge, and Cook 1946; Bennett and Brock 1969; Philp 1974).

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Hilton, J. G., and C. H. Wells. 1976. Influence de l'acide nicotinique sur le volume plasmatique. Perte de la dysbarie expérimentale. Undersea Biomed. Res. 3(2):157-161.– Deux groupes de chiens anesthésiés au pentobarbital du sodium ont été comprimés à 60 psig pendant 60 minutes, et puis décomprimés à une vitesse de 10 psi par minute sans étapes. Le volume plasmatique a été mesuré chez chaque groupe par la technique de dilution de l'albumine marquée à l'I^{131}, avant la compression et 10 minutes et 60 minutes après la décompression. Un groupe d'animaux n'a reçu aucun traitement, tandisque l'autre a recu des injections intraveineuses d'acide nicotinique (15

mg/kg poids corporel juste avant la compression et 7.5 mg/kg poids corporel 30 minutes apres la decompression). Chez les animaux des deux groupes on a constaté des pertes importantes de volume plasmatique 10 et 60 minutes après la décompression, mais les animaux traités avaient perdu moins de plasma (différence significative).

dysbarie — acide nicotinique
substances vasoactives — prostaglandine
perte de volume plasmatique

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