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# EFFECT OF NALOXONE IN HYPOTENSION INDUCED BY ACUTE BLOOD LOSS IN BABOONS (*Papio hamadryas*)

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KEY WORDS: naloxone; opiate receptors; hypotension; *Papio hamadryas*

Injection of naloxone is known to improve the condition of animals with pain-induced, exotoxic, hemorrhagic, endotoxic, and spinal shock [1, 4-6, 8]. This suggests the possibility of clinical use of antagonists of endogenous opioid peptides, which probably play an important role in the genesis of shock states [7], in the treatment of shock.

The object of the present invesgitation was to study the effect of naloxone on the time course of blood pressure (BP), heart rate (HR), and respiration rate (RR) in posthemorrhagic hypotension arising in one of the lower primates that is closest in its medico-biological characteristics to man.

## EXPERIMENTAL METHOD

Experiments were carried out on 11 waking male baboons (*Papio hamadryas*) weighing 7-8 kg. The animals were lightly secured to an experimental platform lying on their back. Under local anesthesia a catheter was introduced into the right superficial lateral subcutaneous vein of the arm. The systolic BP was recorded by Korotkov's method in the left forelimb, HR was determined from the electrocardiogram, RR was recorded by means of a cuff fixed along the costal margin. Bleeding was carried out by removing 40% of the total circulating blood volume at the rate of 10 ml/min (total volume 180-210 ml) through a catheter introduced into the vein of the arm, into preserving solution. Either naloxone solution or physiological saline in a volume of 2 ml was injected through the same catheter 5 min after the end of bleeding, after which the catheter was rinsed with 2 ml of physiological saline. During the first 20 min after injection of naloxone BP was recorded every 30 sec, and during the next 2 h it was recorded three times every 5 min. The animal was reinfused with autologous blood at the end of 2 h.

The results were subjected to statistical analysis by dispersion analysis and Student's t test for small paired samples.

## EXPERIMENTAL RESULTS

Data showing the time course of BP and RR are given in Fig. 1 and Table 1 . HR showed no specific changes in animals of all the groups, and accordingly this parameter was subsequently disregarded. Animals of group 1 (n = 3) were given an injection of physiological saline when BP was reduced by 31.7% as a result of bleeding (control). After injection of physiological saline BP was virtually unchanged, but starting from the 60th-70th minute it began to rise slowly, and by the 120th minute it was already significantly above the posthemorrhagic level, which it exceeded by 24.4%. There was little change in RR, but by the end of 2 h it showed a distinct tendency to fall.

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In the animals of group 2 (n = 4), in which the fall of BP was 33.6%, injection of naloxone in a dose of 1.0 mg/kg during the first 5 min caused a rapid rise of BP by 19.8% that was significant ($P < 0.01$) compared with its values in the animals of group 1, and the peak increase of BP (by 30.4%) was observed after 30 min. During the next 20 min it fell somewhat and before reinfusion of blood began it was indistinguishable from the control. RR in the animals of group 2 showed the same changes after injection of naloxone in a dose of 1.0 mg/kg as in the monkeys of group 1. However, the tendency for RR in the animals of group 2 to decrease was more marked: After a temporary small, but significant ($P < 0.05$) increase compared with the posthemorrhagic level it fell significantly below this level, and at the end of 2 h it was 11.6% lower ($P < 0.05$) than before bleeding.

Group 3 consisted of three animals receiving injections of small doses of naloxone: 0.4, 0,2, and 0.1 mg/kg. The reasons for including them in the same group were, first, the absence of any difference in principle in the time course of the parameters studied, and second, previous observations showing a qualitative difference between the effects of small (0.4 mg/kg) and large (1.0 mg/kg) doses of naloxone in rats with hemorrhagic shock [2].

The fall of BP in the animals of group 3 after bleeding was 21.4%. Levels of BP and RR in animals of all three groups did not differ significantly after bleeding. During the first 5 min after injection of naloxone BP rose by 30.7% and did not differ significantly from the initial level before bleeding; at the end of 2 h it was higher than before injection of the drug. In an animal receiving an injection of naloxone in a dose of 0.4 mg/kg BP was significantly above its initial (before bleeding) level ($P < 0.05$). Meanwhile BP was significantly higher than in the animals of groups 1 and 2 ($P < 0.001$ and $<0.01$ respectively). BP then gradually fell, until the 50th minute, when it was higher than in monkeys of the previous groups ($P < 0.001$ and $<0.01$ respectively). Later BP rose slowly. By the 90th minute after injection of naloxone it was indistinguishable from the BP level in the animals of the first two groups. By the 120th minute BP in animals of group 3 had virtually regained its original (before bleeding) level. RR in these animals showed little change, but there was no tendency for it to fall, and as a result, the significance of the higher values of RR, which became higher after injection of naloxone in a dose of 0.1-0.4 mg/kg, compared with its values in the animals of groups 1 and 2, lasted throughout the period of observation.

Nalorphine was injected in a dose of 1.0 mg/kg into one animal in which BP was lowered by 29.7% after bleeding. Under these circumstances BP rose during the first 5 min by 20.7% and the greatest increase (43.2%) was observed after 40 min, when it did not differ significantly from the initial level. By the 90th minute BP had fallen to its posthemorrhagic level, and this was followed by an increase once again. RR in this animal showed little change, but the absence of any tendency for it to fall must be emphasized (Table 1).

The experiments thus showed that both naloxone and nalorphine effectively raise BP in primates with posthemorrhagic hypotension. Small doses of naloxone (0.1-0.4 mg/kg) have a longer and stronger action under these circumstances than naloxone in a dose of 1.0 mg/kg and they do not depress RR; moreover, there are differences between the temporal parameters of the action of naloxone in different doses. Small doses give maximal effect during the first 5 min after injection, whereas the maximal effect when naloxone is given in a dose of 1.0 mg/kg occurs at the 30th minute. Nalorphine has a more marked action than naloxone in a dose of 1.0 mg/kg, although the temporal parameters of their effects coincide.

These results, and also data in the literature [1-8] suggest that administration both of pure antagonists of endogenous opioid peptides (naloxone) and of mixed antagonists with predominantly antagonistic properties (nalorphine) can be used in clinical practice for the treatment of shock states.

The writers showed previosly [2] that injection of small doses of naloxone (0.4 mg/kg) causes worsening of the course of hemorrhagic shock in rats and on this basis it was postulated that the hypotensive and respiration-slowing effects of endogenous opioid peptides are mediated through low-affinity opiate receptors. Meanwhile the experiments show that small doses of naloxone (0.1-0.4 mg/kg) raise BP in primates more effectively than doses of 1.0 mg/kg. By contrast with rats, in primates receptors with lower affinity for opioids mediate the hypertensive action of endogenous opioids. The improving action of morphine on the course of shock under clinical conditions [3] is probably linked with precisely these receptors. The

TABLE 1. Effect of Naloxone and Nalorphine on Time Course of BP and RR during the Development of Posthemorrhagic Hypotension in Baboons (M ± m)

| Experimental conditions | BP, mm Hg | | | | RR, cycles/min | | | |
|---|---|---|---|---|---|---|---|---|
| | injection of physiological saline | injection of naloxone | | injection of nalorphine 1.0 mg/kg | injection of physiological saline | injection of naloxone | | injection of nalorphine 1.0 mg/kg |
| | | 1.0 mg/kg | 0.1-0.4 mg/kg | | | 1.0 mg/kg | 0.1-0.4 mg/kg | |
| Before bleeding | 163,6±24,9 | 151,1±10,0 | 150,8±1,2 | 157,8±6,3 | 41,3±1,4 | 35,5±6,0 | 42,7±10,9 | 58,2±3,0 |
| After bleeding | 111,7±10,3 | 100,3±5,4 | 118,5±7,8 | 111,0±4,9 | 41,3±12,2 | 40,5±5,3 | 50,2±9,7 | 61,3±1,9 |
| After injection of substance | | | | | | | | |
| 5 min | 100,3±26,2 | 120,2±9,1 | 154,9±11,5 | 134,4±12,8 | 40,7±6,9 | 45,2±7,1 | 55,5±13,7 | 41,0±2,2 |
| 10 min | 102,3±24,7 | 120,7±8,9 | 152,5±12,4 | 137,0±13,0 | 41,0±7,3 | 44,6±7,3 | 54,8±13,7 | 41,6±2,3 |
| 20 min | 114,4±5,6 | 123,9±9,2 | 139,9±11,3 | 145,9±1,6 | 42,7±11,9 | 39,8±5,0 | 49,0±11,4 | 40,0±2,0 |
| 30 min | 112,1±8,4 | 130,8±8,2 | 138,3±12,5 | 158,4±1,7 | 40,8±9,1 | 34,5±7,8 | 50,0±11,7 | 46,0±4,0 |
| 40 min | 115,7±9,7 | 124,4±6,9 | 136,7±12,1 | 159,0±11,0 | 38,5±5,5 | 32,7±8,0 | 49,2±10,1 | 42,5±2,5 |
| 50 min | 114,0±4,5 | 121,3±2,2 | 135,8±11,0 | 140,0±0,0 | 39,0±4,1 | 31,4±6,0 | 48,0±9,2 | 43,5±1,5 |
| 60 min | 118,4±6,2 | 123,5±11,9 | 136,7±11,4 | 145,0±5,0 | 38,3±4,5 | 31,0±5,9 | 48,7±11,1 | 37,0±3,0 |
| 70 min | 123,6±9,4 | 128,1±11,4 | 139,2±13,9 | 135,0±5,0 | 35,3±4,9 | 31,8±5,8 | 43,3±9,3 | 47,0±3,0 |
| 80 min | 123,3±10,0 | 123,9±6,8 | 147,5±7,5 | 125,0±5,0 | 34,2±3,6 | 31,3±4,8 | 48,3±10,5 | 37,0±3,0 |
| 90 min | 133,9±10,1 | 132,5±9,0 | 145,0±10,8 | 112,5±2,5 | 42,0±8,9 | 31,8±6,2 | 50,0±11,7 | 43,0±3,0 |
| 100 min | 138,9±6,8 | 143,1±5,6 | 149,2±6,7 | 117,5±2,5 | 35,2±1,6 | 29,1±6,8 | 49,0±11,0 | 43,0±1,0 |
| 110 min | 135,0±11,2 | 140,7±8,2 | 144,2±12,4 | 132,5±2,5 | 32,7±5,4 | 31,6±5,5 | 45,2±6,8 | 47,0±1,0 |
| 120 min | 139,0±10,8 | 138,9±8,8 | 145,8±8,9 | 127,5±2,5 | 30,8±1,6 | 35,4±6,4 | 47,4±10,4 | 43,0±1,0 |

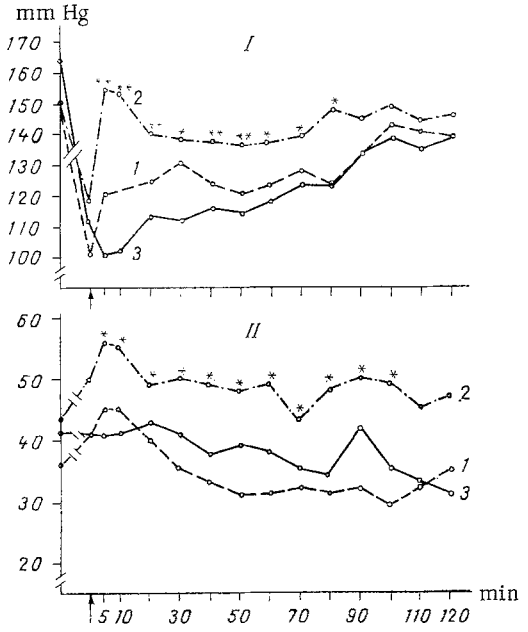


Fig. 1. Changes in BP (I) and RR (II) in baboons after injection of naloxone in doses of 1.0 mg/kg (1) and 0.1-0.4 mg/kg (2) and of physiological saline (3) against the background of hypotension induced by acute blood loss. Differences between groups significant: *P < 0.05; **P < 0.01. Arrows indicate time of injection of substances.

results also indicate a need to take interspecies differences in the role of different types of opiate receptors into account when extrapolating experimental data to man.

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# EFFECT OF ARMIN ON MYELINATED FROG NERVE FIBERS

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Various inhibitors of synaptic cholinesterase are known not only to have a specific action, but also to give rise to other effects [5]. In particular, cholinesterase inhibitors can affect mechanisms of spontaneous and evoked mediator release [2] and the electrogenic membrane of muscle fibers [7]. To understand the mechanism of the blocking of neuromuscular transmission under the influence of anticholinesterase drugs, the effect of these drugs in this manner on the conduction of excitation along fibers must also be evaluated, for it can make a definite contribution to the development of a conduction block.

The object of this investigation was to study the effect of the organophosphorus cholinesterase inhibitor armin (ethyl-p-nitrophenyl ester of ethylphosphinic acid), which has an irreversible anticholinesterase action, on myelinated nerve fibers of the frog *Rana temporaria*.

## EXPERIMENTAL METHOD

Potentials of single Ranvier nodes were recorded by the method of Tasaki and Staempfli. The node for testing was perfused with Ringer's solution or with the test solution, and neighboring nodes, separated from the test node by air gaps, were kept in a solution of 120 mM KCl. For stimulation and recording of potentials Ag-AgCl electrodes were used. The electrode connected to the test node was common for the stimulation and recording systems. The node was stimulated by single square pulses of threshold intensity and duration 0.1 msec. To measure the resistance of the nodes, subthreshold pulses with a duration of 20 msec, a strength of 0.1-0.3 nA, in de- and hyperpolarizing directions, were used. A circuit enabling nodes to be polarized by a dc source, maintaining their membrane potentials (MP) at the level of about −100 mV, also was connected to the stimulating circuit. A buffer resistance of 1 GΩ was included in the circuit for stimulation and polarization, which prevented stimulation of the node by the resting current and stabilized the polarizing current. Potentials were recorded by the dc channel of a UBP2-03 amplifier, the input of which was placed a cathode follower with input resistance of 10 GΩ, input capacitance of 0.55 pF, and grid current of $3 \cdot 10^{-12}$ A. The shunting factor in the recording system was 0.6.

The Ringer's solution used had the following composition (in mM): NaCl 110.5, KCl 2.5, $CaCl_2$ 1.9, Tris-buffer 5.0, pH 7.3-7.4. Test solutions of the same salt composition contained $4 \cdot 10^{-8}$, $4 \cdot 10^{-7}$, $4 \cdot 10^{-6}$, and $4 \cdot 10^{-5}$ M armin. A complete change of solution bathing the node could be done in 15-20 sec. Changes in the test parameters were recorded after 3, 6, 10, and 15 min of action of armin. The nodes were not rinsed after the action of armin. The results were subjected to statistical analysis. Mean values and confidence intervals for P = 0.95 are given in Table 1.

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