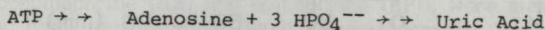


**Title:** DOES ATP-INDUCED HYPOTENSION CAUSE POTENTIALLY SERIOUS METABOLIC COMPLICATIONS?

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Hypotension is often deliberately induced during surgical anesthesia for a variety of reasons. Most commonly sodium nitroprusside is used. However, because of side effects such as tachyphylaxis and cyanide toxicity, other agents have been investigated. Recently some interest has been focused on adenosine triphosphate (ATP) (3,4). In Japan ATP has been reported to be efficacious although the mechanism by which ATP lowers blood pressure has not been established (3,4,5). Adenosine, one of its breakdown products, is known to be a very potent vasodilator, especially of coronary vessels. Consideration of ATP metabolism, however, raises several serious questions, particularly in view of the fairly large doses (relative to endogenous levels) that are necessary to produce the desired decrease in blood pressure. After intravenous administration, ATP is rapidly hydrolyzed to adenosine by the endothelial cells of capillaries (1,2), with the consequent release of three molecules of phosphoric acid.



Adenine nucleotides and phosphate may complex divalent cations such as magnesium and calcium, in addition to altering acid-base status. Adenosine is rapidly deaminated, converted to hypoxanthine, which is then oxidized to uric acid. With prolonged infusion of ATP the final product, uric acid, may accumulate, reaching undesirable levels. Because of these considerations, we have studied the metabolic fate of ATP and its effect in vivo more closely in controlled experiments.

**METHODS.** Male Long Evans rats weighing 250 to 350 g were used. They were anesthetized with halothane in 70% N<sub>2</sub>O - 30% O<sub>2</sub> and femoral arterial and venous catheters were placed. The rats were then allowed to recover for at least one hour in restraining cages. Disodium ATP (100 mg/ml, pH 7.4) was infused into the awake rats at a rate of 10 mg/kg/min body weight for 1 hour. Arterial blood samples were taken at intervals for determination of adenine nucleotides, other metabolites and blood gases. Blood pressure was monitored continuously using a transducer, except when samples were actually being taken.

**RESULTS.** As described by others, infusion of disodium ATP at a rate of 10 mg/kg/min body weight lowered systolic blood pressure by 42 to 56%. Almost immediately upon starting the infusion and in every one of the rats infused, cardiac arrhythmias were detected. These usually took the form of multifocal premature ventricular beats, bradycardia, and bigeminy, and in most animals persisted during the one hour infusion period. These effects may have been due to chelation of magnesium and calcium by either ATP or phosphate. Several rats died within 5 minutes of starting the infusion, with what appeared to be pulmonary edema. The ionized calcium concentration decreased from control values of  $1.02 \pm 0.04$  meq/l (mean  $\pm$  SEM) to  $0.72 \pm 0.01$  meq/l at

60 min. Biochemical analysis of the plasma using sensitive spectrophotometric techniques showed that ATP concentrations were barely detectable throughout the infusion period ( $30 \mu\text{M} \pm 23$  compared to control value of  $18 \mu\text{M} \pm 13$ ), while ADP and AMP were undetectable (less than  $10 \mu\text{M}$ ). Plasma phosphate concentrations rose from  $2.4 \text{ mM} \pm 0.1$  to  $11.5 \text{ mM} \pm 1.2$  at 60 min. This demonstrated that ATP was hydrolyzed at a very rapid rate when introduced into the general circulation. Therefore it seems unlikely that any of the adenine nucleotides could be the active hypotensive agent. Perhaps it is more likely that the product adenosine is involved. Uric acid rose continuously throughout the experimental period from control values of  $2.76 \pm 0.21$  mg/dl to  $9.78 \pm 1.03$  mg/dl. This rather alarming increase would have been greater if it were not for the fact that rats can further convert uric acid to allantoin. (Humans do not metabolize uric acid further.) We also observed changes in acid-base status. During the experimental period, each animal maintained an approximately constant pH. However, pCO<sub>2</sub> decreased by more than 10 Torr at the end of an hour. This resulted from a net base deficit of more than -10 meq/l, due perhaps to hydrolysis of ATP with production of phosphate, or some other unknown effect.

**CONCLUSIONS.** While intravenous ATP appears to have certain advantages for the induction of hypotension, including the absence of tachyphylaxis, the ability to maintain a constant level of blood pressure, and rapid reversibility, there are other aspects which are a cause for concern. These include the persistent appearance of cardiac arrhythmias, changes in acid-base status, and the marked accumulation of the final end product uric acid. If ATP-induced hypotension is maintained for relatively long periods of time, accumulation of the metabolic products may have very serious adverse effects on patient recovery.

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