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Role of hyperuricaemia in critically ill patients especially newborns

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The results of animal experiments and clinical observations concerning the pathological role of hyperuricaemia and the effect of allopurinol treatment in acute metabolic disturbances and critically ill patients is reported.

In uricase enzyme blocked rats treated by oxonic acid, urate nephropathy could be elicited by endogenous purine catabolism in shock. Hyperuricaemia aggravated the shock, while allopurinol increased the survival time. In shock resistant rats hyperuricaemia did not develop when shock was elicited. Allopurinol prevented hyperuricaemia and increased the physical performance of swimming rats, while in experimental DIC allopurinol reduced markedly the hyperuricaemia and the kidney damage.

In clinical studies a close correlation was observed between the degree of hyperuricaemia and the severity of illness. Serum uric acid values were lowered in cases treated by peritoneal dialysis. In randomized control studies of newborns with IRDS the survival rate was improved by allopurinol treatment.

In critically ill patients with various illnesses allopurinol prevented the progression of the pathological process and improved the clinical condition.

The effect of allopurinol in acute clinical metabolic disturbances may be due to its protection against the renal damage by hyperuricaemia and against purine loss by inhibition of xanthine oxidase during the hypoxic stress and the enhancement of hypoxanthine salvage by HGPRT. Allopurinol reduced the production of superoxide radicals and thus the effect of injury may also be moderated by xanthine oxidase blockade.

We have studied the pathological importance of hyperuricaemia (HU) in acute clinical conditions on the basis of the earlier observation that HU was a regular finding in acute shock-like syndromes [2, 6, 11]. It was assumed that HU was not only accompanying acute metabolic disturbances but also an important pathological factor driving the events towards the irreversible stage. The present paper gives a survey of our experiments and clinical observations on the subject.

Materials and Methods

Animal experiments.

Rats treated with oxonic acid (OA) were used as experimental models. OA specifically blocks the uricase enzyme of the animals whose purine metabolism thus becomes similar to that of man. The final degradation product of purines is uric acid. OA and its potassium salt were prepared by the method of Brandenberger [7]. The compound was administered intraperitoneally in 10% solution in four doses of 250 mg/kg at two hour intervals.

Allopurinol (Ap) (Milurit®, EGyT, Budapest) was administered in a dose of 100

mg/kg by gastric tube 12 h and 1 h before tourniquet application.

The serum and kidney acid contents were determined by the method of Kalckar [16].

HU, uric acid nephropathy in uricase blocked rats in shock. (Experiments performed in collaboration with P. Pénzes, Á. Gecse, K. Streitman, E. Zsilinszky, and I. Karády).

The animals used in these experiments were 150–250 g R-Amsterdam rats. Sublethal shock was induced by the procedure of Stoner [26] by arresting the circulation completely in the two hind limbs for 2 h.

A total of 63 rats were divided into five groups: Group I, untreated animals; Group II, rats treated with OA; Group III, animals in tourniquet shock for 2 h and killed 8 h later; Group IV, animals treated with OA as in Group II, and in shock elicited as in Group III, then killed 4 h after release of the tourniquet; Group V, like Group IV, but killed after release of the tourniquet only in the terminal stage (6–14 h).

HU in OA treated shock; its prevention by Ap (Study in collaboration with I. Virág, E. Zsilinszky, and Z. Toldy).

The animals used in these experiments were 160–180 g CFY rats. A total of 30 animals were used. A tourniquet was applied on the two hind limbs for five hours. The experimental groups were, Group VI, shock; Group VII, shock and OA treatment; Group VIII, like group VII, but treated with OA and Ap.

HU and uric acid nephropathy in OA treated shock resistant rats (Experiments in collaboration with I. Karády, E. Zsilinszky, P. Pénzes, K. Streitman, and Á. Gecse.)

A total of 80 R-Amsterdam rats of 180–200 g were used. The experimental groups were Group IX, OA treated controls; Group X, shock by 2 1/2 h tourniquet; Group XI, OA treatment and shock; Group XII, animals made resistant to shock by repeated tourniquet application for 2 1/2 intervals of 48 h. The animals after 24 h were bled then the serum and renal tissue uric acid levels were determined, and the degree of renal uric acid precipitation registered.

Effect of Ap treatment on HU and on physical performance of OA treated swimming rats (Experiments made with the collaboration of I. Virág and Z. Toldy).

A total of 70 CFY rats of 240–380 g was used. They were made to swim by the method of Frenkl et al [12] with a load of 5 g/100 g body weight. The performance was characterized by the time when they definitely sank. Then from the dead animals blood was taken to determine the uric acid level. Experimental groups: Group XIII, control animals; Group XIV, OA treatment; Group XV, OA and Ap treatment; Group XVI, Ap treatment.

Effect of Ap treatment on disseminated intravascular coagulation (DIC) in OA treated rats (Experiments in collaboration with J. Streitman, E. Eck, A. Mágori, and I. Török).

A total of 80 CFY rats of 150–250 g were used. DIC was produced by simultaneous i.p. administration of 0.5 ml of 40% epsilon-aminocaproic acid (EACA) and 1000 U thrombin every hour. Six hours later, after bleeding the animals, uric acid precipitation in the kidneys and the serum uric acid contents were determined.

Experimental groups: Group XVII, control animals; Group XVIII, animals with DIC; Group XIX, animals with DIC treated with OA; Group XX, animals with DIC treated with OA and Ap.

Clinical Examinations

Ap was given orally or the substance was dissolved by the method of Kann et al [17] and given in i.v. infusion. The serum uric acid level was determined by the method of Morin [19] as modified by us [21]. The serum Ap level was estimated by our own method based on the spectrophotometric measurement of xanthine oxidase inhibition of Ap and alloxanthin in vitro [20]

HU and the severity of clinical shock Serum uric acid determinations were done

in 120 children treated for different acute diseases in the intensive ward.

HU in IRDS, and the effect of peritoneal dialysis on HU (Examinations in collaboration with L. Murányi).

A total of 60 newborns was examined. Difficulties of neonatal adaptation where the early symptoms of respiratory disturbance had disappeared within 24 h were considered as transitory tachypnoea; the IRDS II group consisted of those who needed no CPAP or PD treatment as the administration of 0.6 FiO_2 was sufficient to keep the PaO_2 level above 6.5 kPa. If oxygenation did not reach this level, the case was qualified as IRDS and a randomized CPAP or PD treatment was given.

Effect of Ap treatment in IRDS (Examinations in collaboration with I. Németh, P. Hencz, and K. Dénes).

The diagnostic criteria of IRDS were the same as above, i.e. beside characteristic symptoms the patient was qualified as IRDS if the PaO_2 level could not be kept above 6.5 kPa with 0.6 FiO_2 treatment. In such cases, traditional CPAP treatment was instituted, combined if necessary, with PD therapy. Additional Ap was given orally in a dose of 20 mg/kg/day.

Parenteral Ap treatment in critically ill children in need of intensive care (Studies in collaboration with I. Németh).

Intravenous Ap was administered in a dose of 5–10 mg/kg daily with a continuous control of the level of the drug and its active metabolite in the blood in 12 infants or children in a ciritical condition resulting from various illnesses.

Results

Animal experiments

It appears from Table I that when sublethal shock was induced simultaneously with OA treatment (Groups IV and V) the serum and kidney tissue uric acid levels increased considerably. The changes were highly significant statistically. In these animals uric acid precipitation in the kidney was observed in every case.

As Table II and Fig. 1 show, Ap treatment moderated the severity of HU and completely prevented the uric acid nephropathy in OA treated rats in lethal tourniquet shock. It also induced a significant increase in survival. Uricase blockade in the OA treated group resulted in increased lethality as compared to animals subjected to tourniquet shock alone.

Table I

Uric acid contents of serum and renal tissue and the degree of uric acid precipitation in the kidneys in oxonic acid treated rats in shock

Group	No. of animals	Uric acid (mean and standard deviation)		Uric acid precipitation in the kidneys. No. of positive cases and score	
		Serum μmol/l	Renal tissue μmol/kg		
I	10	74.9±22.0	648± 315	0/10	Ø
II	15	86.8±24.3	1059± 184	0/15	Ø
III	15	52.9±11.9	1547± 249	0/15	Ø
IV	10	495.0±124.9	3534±1350	10/10	+++
V	13	718.1±130.9	4420±2374	13/13	+++

TABLE II

Effect of allopurinol treatment on hyperuricaemia and the degree of uric acid nephropathy in oxonic acid treated rats in lethal shock

Group	No. of animals	Uric acid (mean and standard deviation) Serum μmol/l	Uric acid precipitation in the kidneys	
VI	10	317.1±107.6	3/7	+
VII	10	1059 ±328	10/10	+++
VIII	10	297.5±103.5	0/10	Ø

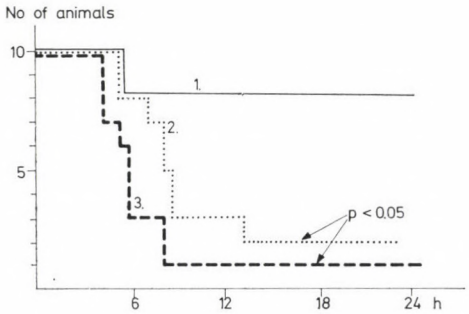

FIG. 1. Survival of shock in rats
1: animals treated with saline, 2: treatment with OA + Ap (uricase and xanthine oxidase blocked rats), 3: OA treated animals (uricase blocked rats)

In rats resistant to shock whose uricase activity was inhibited by OA administration, a less significant increase was observed in the serum uric acid level and no uric acid precipitation occurred in the kidneys, in contrast with the other group which was given the same treatment, but had not been made resistant to shock (Table III).

TABLE III

Uric acid contents of serum and renal tissue and the degree of uric acid precipitation in the kidneys in shock-resistant shocked rats

Group	No. of rats	Uric acid (mean and standard deviation)		Uric acid precipitation in the kidneys. No. of positive cases and score	
		Serum μmol/l	Renal tissue μmol/kg		
IX	5	80.3±21.4	595.0±166.6	0/5	Ø
X	15	99.3±24.9	1112±464	0/15	Ø
XI	20	714.0±124.9	4768±170	20/20	+++
XII	20	127.3±85.6	1304±401	0/20	Ø

TABLE IV

Effect of the allopurinol treatment on hyperuricaemia of oxonic acid treated swimming rats

Group	No. of animals	Uric acid (mean and standard deviation) Serum (μmol/l)
XIII	11	243.9± 73.1
XIV	9	419.4±149.5
XV	8	134.0± 94.6
XVI	14	80.9± 29.7

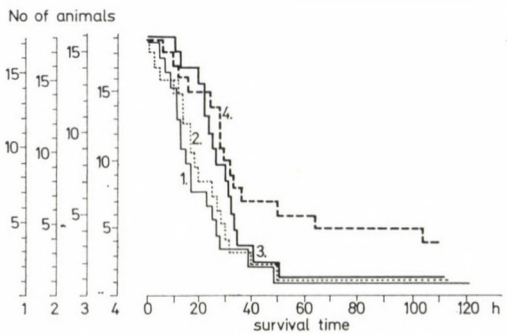

FIG. 2. Survival of rats swimming with a load of 5 g/100 g body weight
1: controls, 2: OA treated animals, 3: OA + Ap treated animals, 4: rats treated with Ap alone. The difference in survival time between groups 1–4 and 2–3 was significant statistically

TABLE V

Uric acid contents of serum and degree of uric acid precipitation in kidneys of oxonic acid treated rats with DIC. Effect of allopurinol treatment

Group	No. of animals	Uric acid in serum (mean and standard deviation) μmol/l	Degree of uric acid precipitation in the kidneys			
			0	+	++	+++
XVII	20	204.6± 96.4	20	Ø	Ø	Ø
XVIII	20	333.7±163.0	20	Ø	Ø	Ø
XIX	20	1044.0±395.0	4	5	8	3
XX	20	315.2±160.6	17	3	0	0

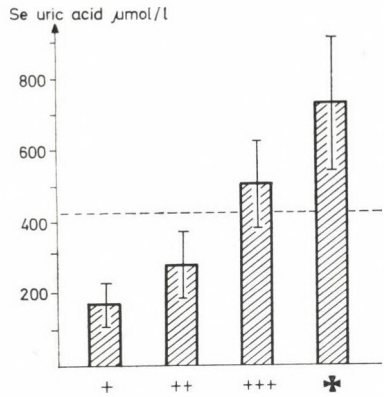

FIG. 3. Serum uric acid level of infants and children with different acute diseases +: cases without severe symptoms, ++: moderately severe and severe cases, +++: critically ill patients. ✠: cases with fatal outcome. Blood taken immediately after death. Dotted line: concentration of serum saturated with uric acid. Potential danger of production of uric acid microcrystals

According to Table IV, maximum physical performance provoked significant HU which could be prevented by previous Ap treatment. The data in Fig. 2 show that Ap treatment improved the performance of swimming rats.

Table V shows that HU could be elicited in DIC produced by thrombin and EACA in rats treated with OA. While Ap markedly reduced the HU, the kidney damage was also less intensive.

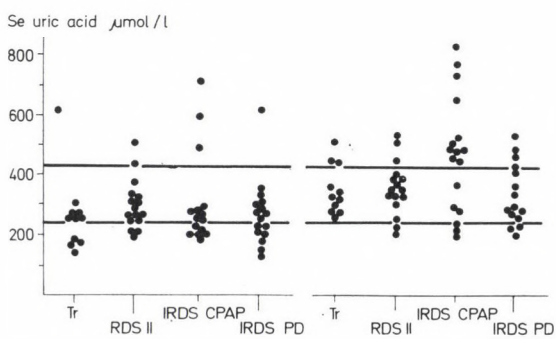

FIG. 4. Serum uric acid level in newborn infants with adaptation disturbances TR: transitory respiration distress syndrome (RDS). RDS II. Mild cases of RDS no needing respiration therapy. IRDS CPAP: IRDS cases needing distending pressure treatment. IRDS PD: IRDS cases treated with peritoneal dialysis. Left side: serum uric acid levels at admission. Right side: Highest serum uric acid levels measured during treatment. Upper line: potential danger of uric acid microcrystal precipitation. Lower line: upper limit of serum uric acid level in healthy preterm newborn infants

TABLE VI

Mortality rate of control and allopurinol treated preterm infants with IRDS

	No. of patients		Lethality per cent
	with IRDS	died	
Control group	56	22	39.3
Allopurinol treated group	50	9	18.0
Statistical significance	$p < 0.05$		

Clinical studies

As it can be seen in Fig. 3, HU was regularly found in patients under intensive care and there was a close correlation between its degree and the severity of the condition irrespective of the basic disease.

Figure 4 shows the blood uric acid levels in newborns suffering from respiratory adaptation troubles. In the most serious cases HU was > 400 μmol/l at admission, a dangerous value from the point of view of renal damage. The level increased parallel with progression of the illness. The fact that lower serum uric acid values were found in the PD treated group may suggest that one component of the favourable effect of PD consists of the moderation of HU.

Considering the results of earlier examinations, we felt it necessary to study whether Ap treatment aiming at xanthine oxidase inhibition would improve the life expectancy of newborns with IRDS. As Table VI shows, Ap treated newborns with IRDS presented an improved survival rate. The difference between the treated and the control group proved to be significant statistically.

Further data showed that the decreased mortality rate of infants with IRDS was accompanied by a decrease in the the serum concentration and urinary excretion of uric acid. In these patients a concomitant improvement of renal function, as indicated by an increased rate of urinary flow, creatinine and sodium output, was also obvious. These data will be published elsewere [5].

Based on the above results it seemed justified to apply Ap treatment in critically ill patients whose clinical condition deteriorated progressively in spite of previous intensive therapy. Ap was given i. v. under a regular control of the blood Ap level.

From the 12 seriously ill patients all but one recovered. The treatment prevented the progression of the pathologic process, the patients' condition improved and a quick decrease of the previously extremely high blood urate was observed. No harmful side effects were noticed [4].

DISCUSSION

The present results seemed to confirm our assumption that HU occurring regularly in acute conditions is

not only a symptom but also an important part and an aggravating factor in the pathologic process of shock. The conclusions may be summarized as follows.

Blockade of uricase by OA [15] is an excellent experimental model for the study of the role of HU in clinical conditions. Urate nephropathy provoked by endogenous purine catabolism in shock may explain the particular inclination of humans to shock since the human organism possesses no uricase. HU aggravates the shock, while Ap treatment increases the survival of shock. It was remarkable that in stressful conditions otherwise leading to HU, in shock resistant animals no significant increase occurred in the serum uric acid level. Ap given in a therapeutic dose to prevent HU, increased the performance in rats exposed to maximum physical load

These results and observations of the role of HU in newborns suffering from adaptation disturbances and in children under intensive care have made us to apply Ap treatment in such clinical situations. The idea was supported by a number of studies on the importance of HU in human pathology, the role of purine degradation in shock or hypoxic processes [9, 14, 17, 23, 24, 25] and partly with the protective role of Ap in tissue ischaemia and consecutive hypoxia [1, 8, 10, 27]. During treatment the blood level of Ap and its active metabolites was regularly controlled.

Since there was no control group, we cannot affirm the efficacy of Ap treatment. A similar study in newborn infants suffering from IRDS was, however, performed in randomized control experiments. The favourable results obtained so far seem to suggest the use of Ap in similar clinical conditions but to corraborate it, further research is needed.

It is assumed that the favourable effect of Ap may be largely due to its protection against renal damage by HU and to the prevention of the intravascular coagulation induced by increased uric acid production.

Once degradation of a nucleotide to uric acid has proceeded beyond the xanthine-hypoxanthine level, it becomes irreversibly lost from the nucleotide pool. Prevention of the purine loss by inhibition of xanthine oxidase preserves the nucleotide pool during the hypoxic stress. The reutilization of oxypurines, suggested by the decrease in the total purine loss, is economical, because the energy requirement (ATP) for de novo purine synthesis is 6 times higher than that needed for reutilization.

Results of recent isotope studies suggested that enhanced purine salvage, in other words the reutilization of hypoxanthine through the enzyme hypoxanthine-guanine-phosphoribosyltransferase (HGPRT), during Ap treatment is an important property in humans [10]. An enhanced hypoxanthine salvage by HGPRT will increase purine nucleotide synthesis and decrease the de novo synthesis of purine, which is regulated through feed-back inhibition by the nucleotide pool. Thus a decrease of de novo purine synthesis may occur secondarily

to increased hypoxanthine salvage [20]. This mechanism provides some assurance that the previously proposed inhibition of de novo purine synthesis may be a less dangerous consequence of Ap therapy in premature infants.

The therapeutic effect of Ap in hypoxic conditions is considered to exert a beneficial effect against ischaemia by preventing the loss of purine bases from hypoxic cells. More recent results suggest that the superoxide radical, an unstable and cytotoxic form of molecular oxygen, has a role in the pathogenesis of ischaemic mucosal lesions and that the enzyme xanthine oxidase is the source of superoxide radicals in the ischaemic small bowel [13]. The studies of Parks et al [22] using Ap indicated that the xanthine oxidase inhibition provides about the same degree of protection of the mucosa from ischaemic injury as that afforded by superoxide dismutase. The findings with Ap strongly support the hypothesis that xanthine oxidase is the source of superoxide in intestinal ischaemia [22].

According to recent experimental data, hypoxanthine and oxygen in combination are destructive to lung tissue, possibly due to an increased amount of free radicals [25]. Hypoxanthine accumulates in neonatal hypoxia, and free radicals can be produced during resuscitation with oxygen [25]. Thus, inhibition by Ap of xanthine oxidase, which also catalyses the formation of superoxide radicals, may be of some advantage.

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The detailed documentation of the experiments has been published in Hungarian periodicals. The author will be glad to supply their reprints on request.

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