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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of intravenous ATP in cancer patients

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Abstract *Objective*: To characterise the pharmacokinetics of adenosine 5′-triphosphate (ATP) in patients with lung cancer after i.v. administration of different ATP dosages.
Methods: Twenty-eight patients received a total of 176 i.v. ATP courses of 30 h. Fifty-two infusions were given as low-dose infusions of 25–40 μg kg^{-1} min^{-1}, 47 as middle-dose infusions of 45–60 μg kg^{-1} min^{-1} and 77 as high-dose infusions of 65–75 μg kg^{-1} min^{-1} ATP. Kinetic data of ATP concentrations in erythrocytes were available from 124 ATP courses. Results are expressed as mean ± SEM.
Results: Most ATP courses in cancer patients were without side effects (64%), and side effects occurring in the remaining courses were mild and transient, resolving within minutes after decreasing the infusion rate. Baseline ATP concentration in erythrocytes was 1554 ± 51 μmol l^{-1}. ATP plateau levels at 24 h were significantly increased by 53 ± 3, 56 ± 3 and 69 ± 2% after low-dose, middle-dose and high-dose ATP infusions, respectively. At the same time, significant increases in plasma uric acid concentrations were observed: 0.06 ± 0.01, 0.11 ± 0.01 and 0.16 ± 0.01 mmol l^{-1}, respectively. The mean half-time for disappearance of ATP from erythrocytes, measured in five patients, was 5.9 ± 0.5 h.
Conclusions: During constant i.v. infusion of ATP in lung cancer patients, ATP is taken up by erythrocytes and reaches dose-dependent plateau levels 50–70% above basal concentrations at approximately 24 h.

Key words ATP · Pharmacokinetics · Cancer

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Introduction

Extracellular adenosine 5′-triphosphate (ATP) is involved in the regulation of a variety of biological processes, including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilatation and liver glycogen metabolism. ATP can be released from the cytoplasm of several cell types and interacts with P1 and particularly P2 receptors on the surface of many cells. These receptors play a fundamental role in cell physiology and are also a potential target in the treatment of various diseases, including paroxysmal supraventricular tachycardias [1], pulmonary hypertension [2], shock [3] and pain syndromes [4]. Furthermore, there is evidence that ATP administration may inhibit the growth of tumour cells and implanted tumours [5, 6].

The range of physiological ATP concentrations within mammalian cells is 1500–4800 μmol l^{-1}. ATP content in tissue cells is somewhat higher than in blood cells [7]. In human erythrocytes, ATP concentrations have been described to be between 1500 μmol l^{-1} and 1900 μmol l^{-1} [8, 9, 10]. Much lower ATP concentrations have been reported for human plasma, in general a factor of 1000 below erythrocyte ATP concentrations [11, 12].

When adenine nucleotides are administered i.v., the nucleotides are taken up by erythrocytes [13]. Using suspensions of washed intact human erythrocytes and labelled purines, Parker et al. [14] found that ATP was metabolised outside the cell via ADP and AMP to adenosine. Adenosine rapidly entered the erythrocytes, where it was incorporated into adenine nucleotides. At extracellular adenosine concentrations below 3 μmol l^{-1},

most intracellular adenosine was phosphorylated to adenine nucleotides, whereas at higher extracellular adenosine concentrations, adenosine was degraded to inosine and hypoxanthine within the erythrocytes [15].

There is little information about pharmacokinetics of administered ATP in humans. In a phase-1 study, Haskell et al. [16] measured whole blood levels of ATP during 96 h of continuous i.v. ATP infusions in 14 patients with advanced cancer of different tumour types. Continuous ATP infusion of 50 $\mu g\ kg^{-1}\ min^{-1}$ induced a mean 63% increase in whole blood ATP levels in these patients after 24 h. A higher dose of ATP infusion of 75 $\mu g\ kg^{-1}\ min^{-1}$ gave only a marginally greater increase (67%). This study, however, did not provide information on the time interval until plateau values were reached. Furthermore, no study has attempted to determine washout parameters of ATP from blood cells.

Recently, in a randomised clinical trial in patients with advanced non-small cell lung cancer, we demonstrated that ATP infusions contribute to maintenance of body weight, muscle strength and quality of life in these patients [17]. The present pharmacokinetic study was aimed at investigating the ATP increase in erythrocytes during i.v. ATP infusion at different doses in patients participating in this trial. Furthermore, we wanted to determine the half-time ($t_{1/2}$) of disappearance of ATP from erythrocytes, which is needed to design an optimal dosing schedule. Finally, we attempted to measure changes in ATP concentrations in plasma during ATP infusion.

Methods

Patients

The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam. Written informed consent was obtained from each individual prior to the study. In the ATP group, there were 28 patients (20 male and 8 female) with locally advanced and metastatic non-small cell lung cancer (stage IIIB/IV), of mean age 64 years (range 30–85 years) and weight 75 kg (range 54–133 kg). None had respiratory, cardiac, hepatic or renal failure. Baseline characteristics of the patients are listed in Table 1.

Design

A maximal number of ten ATP courses of 30 h duration were given: the first seven courses at 2-week intervals and, thereafter, three courses at 4-week intervals. Eleven patients received one to three ATP courses, 5 patients four to six and 11 patients seven to ten.

ATP treatments were started after an overnight fast of 10–12 h, between 0900 hours and 1100 hours. ATP was infused over 30 h through a peripheral vein using an AVI270CI infusion pump. ATP infusions were started at 20 $\mu g\ kg^{-1}\ min^{-1}$ and increased by increments of 10 $\mu g\ kg^{-1}\ min^{-1}$ every 30 min until the maximum dose of 75 $\mu g\ kg^{-1}\ min^{-1}$, or until the maximally tolerated dose (MTD), if this was lower, had been reached. Thereafter, ATP was infused at a continuous rate. If any side effects occurred, the dose was reduced to the last given dose or further until side effects disappeared. Occurring side effects were registered systematically.

Table 1 Baseline characteristics of the patients

Patient no.	Tumour stage	Gender	Age (years)	Weight (kg)	Haematocrit (l/l)	Erythrocyte ATP ($\mu mol\ l^{-1}$)	Plasma uric acid ($mmol\ l^{-1}$)
1	3B	Male	71	79.0	0.31	1261	0.27
2	3B	Male	73	55.8	0.31	1535	0.27
3	3B	Male	74	70.8	0.43	1698	0.29
4	3B	Female	60	61.7	0.40	–	0.31
5	3B	Male	76	89.6	0.48	1071	0.37
6	3B	Male	48	79.7	0.39	1431	0.31
7	3B	Male	41	87.9	0.32	1581	0.26
8	3B	Male	46	80.2	0.34	1850	0.48
9	3B	Male	85	53.9	0.40	1423	0.28
10	3B	Male	71	71.0	0.44	1771	0.34
11	3B	Male	54	74.5	0.45	1624	0.40
12	3B	Female	65	133.0	0.38	–	0.36
13	3B	Male	77	81.6	0.40	–	0.26
14	4	Female	62	68.2	0.38	1553	0.34
15	4	Male	69	70.8	0.39	1921	0.38
16	4	Male	30	71.6	0.32	1981	0.50
17	4	Male	82	75.4	0.40	1500	0.33
18	4	Male	73	60.2	0.37	1768	0.51
19	4	Female	71	74.7	0.41	1385	0.28
20	4	Male	77	66.6	0.33	1327	0.25
21	4	Female	52	65.0	0.42	1538	0.37
22	4	Female	57	57.5	0.31	2069	0.24
23	4	Male	66	68.4	0.36	1311	0.46
24	4	Female	53	69.0	0.31	1703	0.19
25	4	Male	68	114.2	0.47	1117	0.31
26	4	Male	68	65.5	0.41	1483	0.38
27	4	Female	62	68.8	0.29	1664	0.28
28	4	Male	67	73.3	0.34	1285	0.42

Sampling

Prior to ATP administration and at 4, 7, 12, 24, 28 and 30 h after starting ATP infusion, venous blood was sampled from the arm opposite to that in which ATP was infused and was collected into tubes containing ethylenediamine tetraacetic acid (EDTA). One half of the blood samples was immediately placed into separate cryo-tubes, then frozen in liquid nitrogen at −80 °C. The other half was immediately centrifuged for 10 min 1300 ×*g* at 4 °C. Samples of plasma were also placed into separate cryo-tubes, then frozen in liquid nitrogen at −80 °C. In order to obtain a more detailed estimate of the time–concentration relationship and the washout rate of ATP, in five patients, blood samples were drawn after shorter time intervals during both the ATP course and the 12 h after termination of the ATP infusion. Uric acid levels were measured at 0, 24 and 30 h after starting ATP infusion. Information about the rate of renal uric acid clearance (CL_R) was obtained from six patients who collected urine during the 24 h before treatment and the 30 h while ATP was being infused.

Chemicals

Adenosine 5′-triphosphate (ATP-$Na_2 \cdot 3H_2O$) of more than 98% purity was obtained from Merck (Darmstadt, Germany) in 50-g vials; 6.1 g ATP was dissolved in 1 l 0.9% NaCl, sterilised by ultrafiltration (0.2 μM) and supplied in sterile glass bottles. As tested by the method using hexokinase and glucose-6-phosphate dehydrogenase [18], the obtained ATP solution was stable for at least 5 months at −20 °C, and more than 5 days at room temperature. Perchloric acid (71%) and other chemicals were also from Merck.

Laboratory analyses

Whole blood and plasma samples were deproteinised by the addition of perchloric acid to obtain a final concentration of 4% and centrifuged for 10 min 14000 ×*g* at 4 °C. The supernatant was neutralised (pH 6–7) with 2 mol l^{-1} K_2CO_3 in 6 mol l^{-1} KOH, and the sample was kept cold to precipitate the potassium perchlorate. After storage at −20 °C, the supernatant was taken for high-performance liquid chromatography (HPLC) analysis of ATP. Analyses were performed on a Shandon Hypersil ODS (C18) column (150 mm × 4.6 mm; 3 U) with a flow rate of 1.0 ml min^{-1} at room temperature, using a 0.1 mol l^{-1} phosphate buffer (pH 6.0) as eluent. Identification and quantification of the samples was performed by comparing peak areas with appropriate standards. Peaks were detected by absorption at 254 nm and were identified by retention time [19]. Because ATP concentrations in erythrocytes have been reported to be a factor of 1000 above plasma ATP concentrations [11, 12], ATP concentration levels in the erythrocytes were calculated by dividing measured ATP concentrations in whole blood by individual haematocrit values.

Side effects

Side effects were monitored according to common toxicity criteria (National Cancer Institute), scaled on a four-point scale according to seriousness. In this system, dyspnoea is graded as follows: 0, no change; 1, not defined; 2, dyspnoea on significant exertion; 3, dyspnoea at normal activity; and 4, dyspnoea at rest. In general, toxicity was graded as: 1, mild; 2, moderate; 3, severe; and 4, life-threatening.

Pharmacokinetic analysis

Results are expressed as mean ± SEM. Results of independent groups were tested for significance using the Student's *t*-test, and changes in time using the Student's paired *t*-test. *P* values of less than 0.05 indicated significance. The correlation between variables was analysed using a partial correlation coefficient controlling for patient. The $t_{1/2}$ value of ATP disappearance from erythrocytes was calculated for each patient individually by fitting a mono-exponential curve to the washout data, using the software program MicroMath Scientist (Salt Lake City, Utah).

Results

Dosage and side effects

Twenty-eight patients received a total of 176 ATP courses. Seventy-seven infusions were given as high-dose infusions of 65–75 μg kg^{-1} min^{-1} ATP. Because of lower MTD, 47 infusions were given as middle-dose infusions of 45–60 μg kg^{-1} min^{-1} ATP and 52 as low-dose infusions of 25–40 μg kg^{-1} min^{-1} ATP. Side effects observed during the ATP infusions are reported in Table 2. The most frequent side effects were chest discomfort (15%) and the urge to take a deep breath (10%), which resolved within minutes after lowering the ATP dose. Electrocardiography (ECG) was performed in patients with chest pain/discomfort during ATP infusions. No ECG changes suggestive of myocardial ischaemia were detected. The reactions were most common in patients with a history of cardiovascular dysfunction or chronic obstructive pulmonary disease. Heart rate decreased from mean 87.7 ± 1.4 beats/min at baseline to 85.4 ± 1.4 beats/min at 24 h of ATP infusion ($P < 0.05$). Systolic blood pressure decreased from 129.2 ± 1.8 mmHg to 127.1 ± 2.0 mmHg (n.s.), and diastolic blood pressure from 74.7 ± 0.8 mmHg to 71.8 ± 1.0 mmHg ($P < 0.005$).

Erythrocyte ATP levels before and during ATP administration

Kinetic data of ATP concentrations in erythrocytes were available from 124 courses in 23 patients. In erythrocytes, the baseline ATP concentration prior to the first ATP course was 1554 ± 51 μmol l^{-1}. Mean baseline ATP concentrations prior to subsequent ATP courses

Table 2 Side effects ascribed to adenosine 5′-triphosphate (ATP) during a total of 176 i.v. ATP cycles (25–75 mg kg^{-1} min^{-1}) in 28 patients; CTC-grading. In some courses more then one side effect was observed

	CTC grade				
	0	1	2	3	4
Palpitations	174	2	0	0	0
Cardiac ischaemia	176	0	0	0	0
Chest discomfort	150	25	1	0	0
Sweating	171	5	0	0	0
Flushing	168	8	0	0	0
Injection side reaction	172	0	4	0	0
Nausea	168	8	0	0	0
Epistaxis	175	1	0	0	0
Lightheadedness	170	6	0	0	0
Mood alteration; anxiety	173	3	0	0	0
Headache	171	5	0	0	0
Dyspnoea	171	0	0	0	5
Take a deep breath	158	18	0	0	0

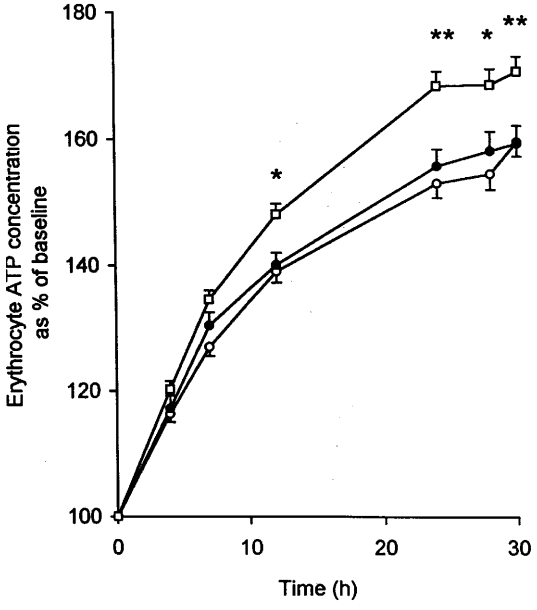

Fig. 1 Erythrocyte adenosine 5′-triphosphate (ATP) concentrations before and during i.v. ATP administration. Values are expressed as a percentage of baseline at ATP dose 25–40 μg kg^{-1} min^{-1} (○, $n = 35$); 45–60 μg kg^{-1} min^{-1} (●, $n = 23$); and 65–75 μg kg^{-1} min^{-1} (□, $n = 66$). Differences relative to middle dose: $^{*}P < 0.05$, $^{**}P < 0.01$. Data are presented as mean values ± SEM

did not show any significant differences from the initial baseline ATP concentrations (data not shown).

We compared the increase in ATP concentrations in erythrocytes during low-, middle- and high-dose ATP infusion. At all time points the mean ATP values were significantly higher than the baseline concentration of ATP ($P < 0.001$).

As seen in Fig. 1, plateau levels of ATP were reached at approximately 24 h. In a subgroup of patients in whom blood was sampled at 2-h intervals, a similar kinetic profile of blood ATP concentrations was observed. Compared with baseline levels, low-dose ATP infusions induced a 53 ± 3% increase in erythrocyte ATP concentrations ($P < 0.001$) and middle-dose ATP infusions a 56 ± 3% increase ($P < 0.001$), whereas high-dose ATP infusions evoked an increase of 69 ± 2% ($P < 0.001$). The rise in erythrocyte ATP concentrations after high-dose ATP infusion was significantly larger than middle-dose ($P < 0.05$) and low-dose ($P < 0.01$) ATP infusions at all times points from 12 h to 30 h. In contrast, erythrocyte ATP concentrations during middle-dose ATP infusions did not differ significantly from those during low-dose ATP infusions. Nevertheless, a moderate overall dose–level relationship was observed at 24 h and 30 h ($r = 0.56$ and $r = 0.49$, respectively, $P < 0.005$).

ATP concentrations in erythrocytes from one patient who received ten successive ATP courses of 75 μg kg^{-1} min^{-1} are plotted in Fig. 2. The standard deviation between erythrocyte ATP levels during the different courses varied from 5% to 9%.

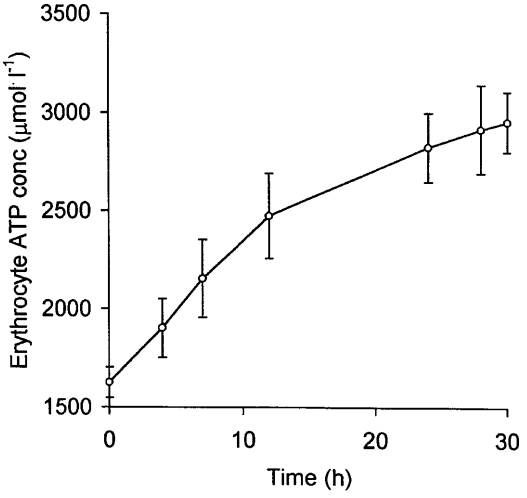

Fig. 2 Erythrocyte adenosine 5′-triphosphate (ATP) concentrations in one patient during ten subsequent ATP courses of 75 μg kg^{-1} min^{-1} given at 2-week to 4-week intervals (see Methods). Data are presented as mean values ± SD

Uric acid concentrations in plasma

Plasma levels of uric acid as a breakdown product of ATP showed a dose-dependent increase after 24 h and 30 h of ATP infusions (Fig. 3). Plasma uric acid concentrations increased by 0.06 ± 0.01 mmol l^{-1} after 24 h during low-dose ATP infusion ($P < 0.001$), by 0.11 ± 0.01 mmol l^{-1} with middle-dose infusion ($P < 0.001$) and by 0.16 ± 0.01 mmol l^{-1} with high-dose ATP infusion ($P < 0.001$). At all doses of ATP

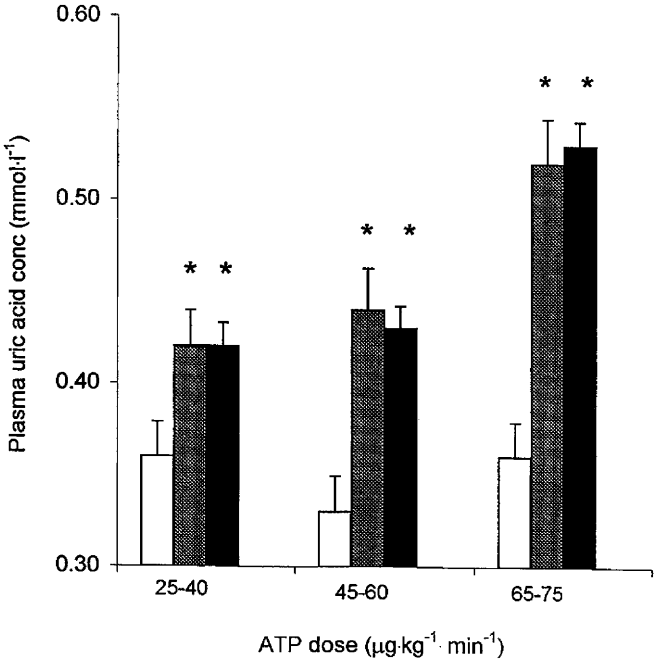

Fig. 3 Plasma uric acid concentrations (mmol l^{-1}) at baseline (*open bars*), 24 h (*grey bars*) and 30 h (*solid bars*) with ATP doses of 25–40 μg kg^{-1} min^{-1}, $n = 35$; 45–60 μg kg^{-1} min^{-1}, $n = 27$; and 65–75 μg kg^{-1} min^{-1}, $n = 43$. Significantly different from baseline: $^{*}P < 0.001$. Data are presented as mean values ± SEM

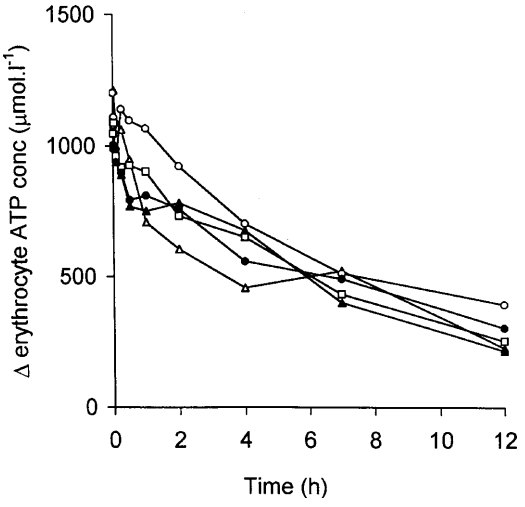

Fig. 4 Erythrocyte adenosine 5′-triphosphate (ATP) concentrations in five patients during washout following 30 h of i.v. ATP administration. Values are expressed as differences from baseline values. *Solid symbols*: after low-dose ATP infusion. *Open symbols*: after high-dose ATP infusion

administration, mean uric acid concentrations at 30 h were almost identical to those at 24 h. A significant ATP dose – uric acid level relationship was observed both at 24 h and 30 h ($r = 0.76$ and $r = 0.81$, respectively, $P < 0.001$). There was a poor relationship between ATP levels in erythrocytes and uric acid levels in plasma, with correlation coefficients of 0.31 at 24 h ($P = 0.07$) and 0.21 at 30 h ($P = 0.08$).

Disappearance of ATP from erythrocytes

Information concerning the rate of disappearance of ATP from erythrocytes after termination of the ATP infusion was obtained in five patients. Figure 4 shows that the rates of ATP disappearance in these patients were approximately similar regardless of ATP infusion doses. ATP concentrations during washout followed a mono-exponential pattern, with a $t_{1/2}$ of 5.9 ± 0.5 h.

ATP concentrations in plasma

In plasma no increases in ATP concentration were shown during ATP infusions. In several patients, the data obtained before and during ATP infusions were highly scattered (range 0.5–8.5 μmol l^{-1}).

Discussion

The aim of the study was to investigate pharmacokinetics of ATP in erythrocytes in patients with lung cancer following i.v. ATP administration. In a subgroup of patients, the disappearance of ATP from erythrocytes in vivo was measured.

The mean baseline concentration of ATP in erythrocytes was 1554 ± 51 μmol l^{-1}, and comparable baseline ATP concentrations were observed prior to the subsequent ATP courses. Mean ATP concentrations in lung cancer patients in this study are in agreement with values reported by Stocchi et al. for ten normal adult controls (1501 ± 25 μmol l^{-1}), but not with their finding of lower erythrocyte ATP concentrations in ten patients with gastrointestinal adenocarcinoma (1099 ± 41 μmol l^{-1}) [20]. We checked ATP values of erythrocytes in normal healthy subjects ($n = 9$) and observed mean values of 1400 ± 60 μmol l^{-1}. Thus, Stocchi's finding of lower erythrocyte ATP in patients with gastrointestinal adenocarcinoma does not seem to apply to patients with bronchus carcinoma.

A cascade of ectonucleotidases on the surface of endothelial cells is thought to be responsible for the hydrolysis of ATP [21–24]. It has been suggested that the ectonucleotidases may regulate plasma nucleotide levels [25] and, thus, have a protective function by keeping extracellular ATP and adenosine levels within physiological limits [13]. Three types of ectonucleotidases have been described: ecto-ATPases, ecto-ADPases and ecto-5′-nucleotidases [13]. In blood, these enzymes have also been detected on erythrocytes [13], leukocytes [25], B-lymphocytes [26], and both helper and cytotoxic T-lymphocytes [27]. In the extracellular space, ATP is subject to breakdown by ecto-enzymes and xanthine oxidase to form uric acid which is excreted in urine. In the present study, continuous ATP infusions induced significant and dose-dependent increases in erythrocyte ATP concentrations with plateau levels between 24 h and 30 h. This is in line with the findings of Haskell et al., who infused ATP for 96 h and observed no further rise of ATP in erythrocytes after 24 h of ATP infusion [16]. Uric acid plasma concentrations at 24 h and 30 h were increased when compared with initial uric acid plasma concentrations.

Low-dose ATP infusions (25–40 μg kg^{-1} min^{-1}) induced a significant increase in erythrocyte ATP concentrations parallel with increasing plasma uric acid concentrations. At middle-dose ATP infusions (45–60 μg kg^{-1} min^{-1}), no further rise in erythrocyte ATP concentrations was measured, whereas the degradation of ATP was further increased as demonstrated by a further rise in uric acid concentrations. High-dose ATP infusions (65–75 μg kg^{-1} min^{-1}) induced not only an even larger increase in uric acid levels, but also showed an additional increase in erythrocyte ATP levels compared with low- and middle-dose ATP infusions. In order to exclude the possibility of ATP-induced inhibition of the CL_R of plasma uric acid, we measured the rate of uric acid clearance in six patients who collected urine before and during ATP infusion. None of these patients who were treated with either low-, middle- or high-dose ATP infusions showed any change in uric acid CL_R ($P = 0.91$; paired t-test).

A strong dose–level relationship was observed between ATP dose and uric acid concentrations in plasma. In the phase-1 study by Haskell et al. [16], ATP-infused subjects received allopurinol as a standard

therapy because the first two subjects treated with ATP developed asymptomatic hyperuricaemia and uricosuria. In the present long-term intervention study, we chose not to give allopurinol, since the risks of asymptomatic hyperuricaemia are known to be small and allopurinol treatment may itself induce side effects such as renal insufficiency, gastric irritation, diarrhoea, skin rash and, occasionally, vasculitis [28, 29].

We found a mono-exponential rate of ATP disappearance from erythrocytes with a $t_{1/2}$ of approximately 6 h. This is in line with the finding of Rapaport et al. [5] that after uptake of ATP by erythrocytes the subsequent release of ATP into plasma is relatively slow. In animal studies, ATP in plasma is rapidly broken down. In these studies, ATP was administered as a bolus, so that erythrocyte ATP levels would increase only slightly. In rabbits, 40 s after an i.v. bolus injection of ATP, only 1% of ATP was detected in whole blood [30]. Similarly, a bolus of ATP was found to be almost completely cleared during a single passage through either perfused dog lung [31] or perfused guinea-pig heart [32]. In a perfused rat lung, Ryan et al. [21] showed a $t_{1/2}$ of labelled ATP of less than 3 s.

The few reports on physiological ATP concentrations in human plasma give mean values ranging from 0.02 μmol l^{-1} [33] to 10.9 μmol l^{-1} [34]. Determination of ATP in plasma is technically difficult as the concentration in plasma is three orders of magnitude lower than within the cells. It is obvious that even limited haemolysis could cause considerable elevation of plasma adenine nucleotides [12] since as little as 0.1% haemolysis during sampling would double the ATP concentration in plasma [12]. In addition, EDTA can induce selective nucleotide release from cells [25]. Other factors influencing plasma ATP measurements may be released from platelets [35], thrombus formation [36], partial arterial occlusion and exercise [33]. Furthermore, the time between venous blood sampling and centrifuging may have a marked influence on plasma ATP concentrations. It is therefore not surprising that we obtained scattered data when attempting to measure ATP in plasma prior to and during ATP infusions.

In conclusion, our study in cancer patients shows that, during continuous ATP infusions in a dose range of 25–75 μg kg^{-1} min^{-1}, ATP is taken up by the erythrocytes and reaches dose-dependent plateau levels within erythrocytes which are 1.5- to 1.7-fold higher than baseline values at approximately 24 h. After discontinuation of the ATP infusion, $t_{1/2}$ of ATP disappearance from erythrocytes was approximately 6 h. ATP infusions can be administered without side effects in the majority of courses, and when side effects occur they are mild and transient. Further study of ATP pharmacokinetics is warranted in order to optimise the ATP dosage scheme for further clinical trials in cancer and other diseases. It would be useful to perform a study with infusions of 25 μg kg^{-1} min^{-1} or 75 μg kg^{-1} min^{-1} ATP, respectively, in order to show whether there are differences in clinical results between low- and high-dose ATP. Courses should have a minimal duration of 24 h to reach a plateau ATP level in erythrocytes. Patients suffering from cardiopulmonary disease may receive low-dose ATP infusion in order to avoid side effects. In view of the observation that hyperuricaemia is only transient and asymptomatic, it seems unnecessary to give allopurinol in parallel with ATP infusions.

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