ATPace™: injectable adenosine 5'-triphosphate

Diagnostic and therapeutic indications

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Abstract ATPace™, a novel injectable formulation of adenosine 5'-triphosphate (ATP), is developed by Cordex Pharma, Inc. (Cordex) as a diagnostic and therapeutic drug for the management of cardiac bradyarrhythmias. Extracellular ATP exerts multiple effects in various cell types by activating cell-surface receptors known as P2 receptors. In the heart, ATP suppresses the automaticity of cardiac pacemakers and atrioventricular (AV) nodal conduction via adenosine, the product of its degradation by ecto-enzymes, as well as by triggering a cardio-cardiac vagal reflex. ATP, given as a rapid intravenous bolus injection, has been used since the late 1940s as a highly effective and safe therapeutic agent for the acute termination of reentrant paroxysmal supraventricular tachycardia (PSVT) involving the AV node. In addition, preliminary studies have shown that ATP can also be used as a diagnostic agent for the identification of

several cardiac disorders including sinus node dysfunction (sick sinus syndrome), dual AV nodal pathways, long QT syndrome, and bradycardic syncope. The US Food and Drug Administration has approved Cordex formulation for ATP as an Investigational New Drug and two pathways for its marketing approval; one therapeutic, i.e., acute termination of paroxysmal PSVT, and the other diagnostic, i.e., the identification of patients with bradycardic syncope who can benefit from pacemaker therapy. The scientific rationale for the development of ATPace™ is discussed.

Keywords Syncope · Bradycardia · Vagus · Cardiac pacing · AV node

Introduction

The ubiquitous purine nucleotide adenosine 5'-triphosphate (ATP) plays a critical role in cellular metabolism and energetics. ATP is released into the extracellular space under physiologic and pathophysiologic conditions [1]. Extracellular ATP is an autocrine and paracrine signaling molecule that activates cell surface purinergic P2 receptors (P2R) [1]. P2R are divided into two main families: P2Y, G protein-coupled receptors and P2X, trans-cell membrane cationic channels [2]. In the heart, ATP exerts a pronounced negative chronotropic effect on cardiac pacemakers and negative dromotropic effect on atrioventricular nodal (AVN) conduction, and a positive relaxation (lusitropic) effect on the coronary vasculature [3, 4]. The negative chronotropic and dromotropic actions of ATP are mediated by adenosine, the product of ATP's rapid degradation by ecto-enzymes (mainly CD39 and CD73) [5] and by a cardio-cardiac vagal reflex triggered by ATP's stimulation

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of vagal sensory nerve terminals in the left ventricle [6]. The potent but transient inhibition of AVN conduction constitutes the rationale for the use of ATP as an anti-arrhythmic drug for the acute termination of reentrant paroxysmal supraventricular tachycardia (PSVT) involving the AV node. Indeed, rapid bolus injections of liquid formulations of ATP have been used since the late 1940s for the acute termination of PSVT and restoration of sinus rhythm [7]. In addition to its therapeutic (i.e., anti-arrhythmic) utility, ATP has also been used as a diagnostic tool for the diagnosis of sinus node dysfunction (SND) [8–12] and long QT syndrome [13], and the identification of the mechanism of cardiac arrhythmias [14]. ATP has also been evaluated as a diagnostic tool in the management of patients with neurally mediated syncope (NMS) as well as in evaluation of syncope of unknown origin (SUO) [15].

ATP as an anti-arrhythmic drug

Because it is a natural compound that is found in every cell of the human body in relatively large amounts, ATP has been administered to human subjects on an empirical basis as a drug candidate for the treatment of multiple ailments since its discovery in 1929. Dr. Ernő Somló of the Postgraduate Institute of Medicine in Budapest, Hungary, first reported in 1955 the successful termination of multiple PSVT episodes with a rapid intravenous injection of 2 ml solution containing 20 mg of ATP [7]. Dr. Somló's rationale for using ATP in this setting was that others before him “made it clear” that ATP “...act[s] by inducing ‘shock’ comparable to that produced, under certain conditions by histamine, adrenaline, or insulin”; he also stated that “accordingly, I have tried, over the past ten years, to bring about the cessation of paroxysmal tachycardia by producing a mitigated shock with intravenous ATP” [7]. In view of the fact that the mechanisms of PSVT were not known at that time, the hypothesis that a systemic shock, albeit a mitigated one, could benefit a patient with PSVT was indeed unfounded. It is unimaginable today that a physician would administer to his/her patients a *shock inducing* compound in such a manner, which is tantamount to unjustified experimentation. Yet, Dr. Somló was not alone in this practice; several other European physicians administered ATP to human patients in this and other similar clinical settings. Early reports on the use of ATP in the acute management of PSVT clearly indicate that the users were not familiar with the mechanism that mediated its beneficial effect. The most common mechanisms of PSVT were only proposed in the mid 1960s based on experimental studies and confirmed subsequently in the clinical setting in the early 1970s [16, 17].

The most common types of PSVT are AVN reentrant tachycardia and AV reentrant tachycardia. In the former type, the reentrant circuit resides solely within the AV node and/or the immediate neighboring cells, and in the latter type, the AV node is part of the reentrant circuit with the remainder of the circuit being comprised of extra-nodal accessory AV connection(s). Accordingly, in both types, acute termination of the tachycardia can be achieved by the induction of a transient complete AVN conduction block. Both ATP and adenosine are highly effective in termination of PSVT due to their depressant effects on AV nodal conduction [18]. However, the mechanism of the negative dromotropic action of ATP and adenosine is not identical. Adenosine depresses AV nodal conduction by direct action on AV nodal cells [19]; in contrast, ATP acts in two ways: first, via adenosine, the product of ATP's rapid degradation by ecto-enzymes, and second, via a cardio-cardiac vagal reflex [20]. The latter, induced by the activation of P2X2/3 receptors in the infero-posterior wall of the left ventricle [21], explains why on molar basis, ATP is much more potent than adenosine [22].

ATP in the diagnosis of bradycardic syncope

In 1986, Flammang et al. [23] were the first to hypothesize that patients, in whom the main cause of syncope was bradycardia, were hypersensitive to ATP. They suggested that ATP (20 mg, rapid i.v. bolus) could be used as a diagnostic tool for the identification of patients with vasovagal syncope who could benefit from pacemaker therapy (what they called the “ATP test”). In 1994, Brignole et al. [24] studied the effects ATP in healthy subjects and in patients with NMS, SND, or both [24]. They found that the depressant effect of ATP on the AV node was more pronounced than that on the sinus node, and the latter was similar in healthy subjects and patients with NMS. However, a more pronounced effect was found in patients with SND and patients with NMS+SND [24]. In addition, the frequency of ATP-induced complete AV block in healthy subjects, patients with NMS, and patients with NMS+SND was 45%, 38%, and 18%, respectively. They interpreted these data to suggest that “the clinical meaning of ATP-induced AV block remains uncertain” [24]. Subsequently, Flammang et al. [25] and Brignole et al. [26] assessed the ATP test as a diagnostic tool for the identification of the mechanism of syncope in patients with NMS or SUO. Other than the identical ATP dose, the two aforementioned studies differed from each other in several critical aspects (Table 1).

Although the results of their initial study led Brignole et al. [26] to conclude that “a logical inference is that ATP testing can be used to identify patients with syncope due to

Table 1 Characteristics of the ATP test employed by Flammang et al. [25] and Brignole et al. [26]

Item	Flammang et al. [23]	Brignole et al. [24]
Driving hypothesis	Bradycardia is due to (1) malfunctioning sinus node, (2) malfunctioning AV node, and (3) abnormal vagal input or any combination of these three factors. A positive test is indicative of bradycardia as the cause of syncope.	Increased susceptibility of the AV node to adenosine may play a role in the genesis of some cases of syncope. A positive ATP test is indicative of AV nodal conduction block as the cause of syncope
Mode of ATP administration	Striadyne® (20 mg ATP/2 ml) given as a rapid bolus followed by 20 ml physiologic solution flush.	Striadyne® (20 mg ATP/2 ml) “dissolved in 10 ml saline solution injected very rapidly”
Quantifying the effect of ATP	A positive ATP test was defined as one, in which the ATP-induced “cardiac pause” (CP) was greater than 10 s, based on the 95 percentile of CP=10 s found in a cohort of healthy subjects. CP was defined as the duration of asystole due to sinus arrest or in the case of transient complete AV node conduction block, the time interval from the first blocked sinus beat to the first three consecutive conducted beats ignoring junctional, infra-nodal, and fusion beats.	A positive outcome of the ATP test was defined as one in which ATP-induced maximal RR interval (RR _m) was greater than 6 s, based on the 95th percentile of the RR _m =6 s during ATP-induced AV block in a cohort of healthy subjects.
Validation of the ATP test	Recurrence of syncope in patients with positive ATP test subjected to pacemaker therapy during follow-up periods.	Correlating the outcome of the ATP test to (1) “the fortuitous ECG recording of a spontaneous syncope caused by a transient asystolic pause”, (2) implantable loop recorder data, and (3) data of the head-up tilt table test.

paroxysmal AVB”, their subsequent studies using also the head-up tilt table test and/or the implantable loop recorder led them to negate the utility of the ATP test as a diagnostic tool in this setting [27–29].

A detailed discussion of the discrepancy between the approaches of the two groups mentioned above and their contrasting views regarding the utility of the ATP test is beyond the scope of this paper. However, it should be noted here that several studies have shown that in a specific cohort of syncope patient, in whom the ATP test was positive based on cardiac pause duration, pacemaker therapy was highly beneficial in preventing syncope recurrence [30–32].

ATPace™: a new formulation of injectable ATP

ATPace™ is a novel liquid formulation of ATP for intravenous administration; it is being developed by Cordex Pharma, Inc. as a therapeutic and diagnostic drug. The proposed indications of ATPace™ are: (1) the acute termination of PSVT and (2) the identification of patients with bradycardic syncope who may benefit from pacemaker therapy.

Stability tests have shown that ATPace™ is exceptionally stable; specifically, after 6-year storage at 4°C, <5% of ATP was hydrolyzed to ADP. The stability of a given liquid formulation of ATP has direct relevance to its potency. Indeed, review of the literature indicates that 6 mg of adenosine and 10 mg ATP terminates ≤60% and ≥70% of the PSVT episodes, respectively; however, because the molecular weight of ATP

is approximately twice that of adenosine, 10 mg of ATP contains fewer molecules than those found in 6 mg of adenosine.

Regarding the therapeutic indication of ATPace™, the US FDA had reviewed the voluminous historical published clinical data submitted by Cordex demonstrating the efficacy and safety of injectable ATP in the acute termination of PSVT. Subsequently, Cordex has reached an agreement with the FDA regarding a Special Protocol Assessment on the design of a phase IIb/III protocol of an ATPace™ safety–efficacy study. Regarding the diagnostic indication, ATPace™ Cordex had successfully completed a phase I maximal tolerable dose study, and commenced a phase II proof-of-concept study in patients with NMS. The latter was designed to reproduce data obtained in Europe indicating that some patients with NMS or SUO are hypersensitive to ATP. By the time this study was suspended in its midst due to slow enrollment rate, 47 patients had been studied: 18 of which were males and 29 females; 10, 24, and 13 patients were 18–24, 35–64, and ≥65 years old, respectively. Analysis of data obtained in these patients has indicated that the clinical endpoint has been reached considering historical control data, i.e., data obtained with ATP in healthy human subjects. Specifically, 10 out of the 47 (21.3%) patients vs. 3 out of 51 (5.9%) healthy subjects studied earlier by Flammang et al. [25] manifested a cardiac pause >10 s ($p<0.05$). Thus, pending the FDA acceptance of this data interpretation, ATPace™ would be ready for a pivotal phase III study aimed at demonstrating the efficacy of pacemaker therapy in preventing syncope recurrence in patients with a positive

ATP test (i.e., demonstrating patients' benefit from the diagnostic test). The design of the latter could parallel that of a recent European multi-center study [32].

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