A Randomized, Double-blind, Placebo Controlled Study of Oral Adenosine Triphosphate in Subacute Low Back Pain

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ABSTRACT. ***Objective.*** To assess the efficacy and safety of oral adenosine triphosphate (ATP) in subacute low back pain.

Methods. This was a randomized, double-blind, parallel group, placebo controlled clinical trial. The patients were given either ATP 90 mg once daily (n = 81) or placebo (n = 80) for one month. The patients were assessed 3 times during the study period, at days 0, 7, and 30. The primary outcome measure was the Roland-Morris Disability Questionnaire (RDQ) at day 30. Secondary measures of efficacy included visual analog scale (VAS) pain, overall assessments of efficacy by both patient and investigator, and number of dextropropoxyphene and acetaminophen combination tablets used as rescue analgesic.

Results. Regarding the RDQ, the mean values dropped from 10.3 ± 2.8 at baseline to 7.5 ± 3.8 (day 7) and 5.2 ± 5.2 (day 30) in the ATP group, and from 11.0 ± 3.5 to 9.1 ± 4.2 (day 7) and 6.1 ± 4.3 (day 30) in the placebo group. The difference between the 2 groups was statistically significant at day 7 (p = 0.02) but not at day 30 (p = 0.2). In other words, the mean changes from baseline were 2.8 ± 3.1 and 2.0 ± 2.6 at day 7 (p = 0.06), and 5.1 ± 3.9 and 5.0 ± 4.2 at day 30 (p = 0.78) in the ATP group and the placebo group, respectively. There were no statistically significant differences in the VAS pain and overall assessments of efficacy between groups at any time point during the study. Conversely, there was a significant difference in the use of the rescue analgesic between groups, in favor of ATP (p = 0.04). Oral ATP was well tolerated.

Conclusion. Oral ATP might have an early acting effect in subacute low back pain. (J Rheumatol 2005;32:1114–7)

Key Indexing Terms:
ADENOSINE TRIPHOSPHATE   PAIN   LOW BACK PAIN

Low back pain (LBP) is a very common disorder with major consequences for health care resources in Western countries. LPB is usually a benign and self-limiting disease. However, its outcome varies according to the duration of symptoms.

The widely held view is that acute forms tend to go into spontaneous remission whereas chronic LBP is rather therapy resistant. In fact, 90% of patients with uncomplicated, mechanical acute LBP recover within 6 weeks and another 5% in 12 weeks[1]. A recently published systematic review of prospective studies confirmed that most people with acute LBP have rapid improvement in pain and disability within 1 month[2]. Further improvement, albeit less pronounced, occurs for about 3 months. Thereafter, levels of pain and disability remain nearly constant until the 12 month followup[2]. Thus, subacute LBP should be considered as a critical stage between acute (< 4 weeks) and chronic (> 12 weeks) states[3].

Although a specific pathologic cause cannot be identified for most episodes of LBP, it is recognized that pain may arise from several structures in the lumbar spine, including the paravertebral musculature[1,4]. Since adenosine triphosphate (ATP) is involved in a broad spectrum of biological functions, including muscular cell function, it was thought that this purine nucleotide would improve muscle functioning, and hence, accelerate recovery in people with LBP[5]. Based on this assumption, oral ATP (Atépadène®) has been proposed in France as an adjunct in the treatment of LBP.

Animal studies indicated that chronic oral administration of ATP produced various pharmacological effects, especially peripheral vasodilatation and alterations in the metabolism of peripheral muscles, which would benefit patients with LBP[6,7]. However, the role of muscle spasm in the pathogenesis of LBP is controversial[8]. Furthermore, little information is available from clinical trials on the effectiveness of oral ATP. Two randomized, double-blind, placebo-controlled trials have shown some efficacy of the compound on pain and functional outcomes with no adverse reactions in patients with uncomplicated back pain[5,9]. Unfortunately, both studies were conducted in patients with either thoracic or lumbar back pain of varying duration and they were published in non-indexed medical journals[5,9]. Notwithstanding the poor knowledge of its effectiveness, oral ATP is widely prescribed by French general practitioners, probably because of its low cost and excellent safety profile, the drug being virtually devoid of any significant side effects or drug-drug interaction.

Our study aimed at evaluating the efficacy of oral ATP in patients with subacute LBP.

MATERIALS AND METHODS

This study was conducted in accordance with good clinical practice guidelines and principles of the Declaration of Helsinki. The protocol was approved by the Bordeaux B Institutional Review Board for the Protection of Human Subjects, France. All patients gave written informed consent to participate.

Patient selection. The study population was recruited from the community by general practitioners. It included men and women aged 18 to 55 years with a diagnosis of subacute LBP of category 1 or 2 according to the classification of the Paris Task Force[3], i.e., LBP radiating no farther than the intergluteal fold (category 1) or the knee (category 2), with no neurologic signs, and lasting from 4 to 12 weeks. Patients were eligible if they had a Roland-Morris Disability Questionnaire (RDQ) score > 6 at study entry [RDQ scores range from 0 (no disability) to a maximum of 24][10]. Important exclusion criteria included LBP related to acute trauma, vertebral fractures, tumors, and inflammatory or infectious diseases affecting the spine. Patients with a history of spine surgery, lumbar corticosteroid injection within 3 months prior to study entry, and ongoing therapy with systemic corticosteroids, antidepressants, or benzodiazepines were also excluded, as were pregnant or lactating women and patients with renal or hepatic insufficiency.

Study design. This was a randomized, double-blind, parallel group, placebo controlled clinical trial. Eligible patients were randomly assigned to receive either 90 mg of oral ATP (Atépadène®, Mayoly-Spindler) once daily according to the product monograph or an identical placebo for 1 month. During the study, patients were permitted to take up to 6 dextropropoxyphene 30 mg-acetaminophen 400 mg combination tablets daily as rescue analgesic, and daily consumption was recorded. Other analgesics, including nonsteroidal antiinflammatory drugs, locally applied or systemic corticosteroids, myorelaxants, and physiotherapy were prohibited. Furthermore, patients were recommended to avoid bed rest and they were advised to maintain or resume their normal activities, as far as pain allowed[3].

Efficacy and safety assessments. In addition to the screening visit (day 0), visits were scheduled at days 7 and 30. Outcome measures included the French validated version of the RDQ[11], patient assessment of pain on a 100 mm visual analog scale (VAS), number of rescue analgesic tablets used, and patient and investigator global assessments of efficacy on a 4 point scale (largely or slightly improved, unchanged, worse). The primary outcome measure was the RDQ score at day 30. Adherence to trial medication and adverse events were monitored at each trial visit. Safety assessment consisted of inquiries regarding any sign or symptom that a patient may have experienced, and physical examination at each visit.

Sample size and statistical analysis. Roland and Fairbank[12] recommended changes in scores of 2-3 points on the RDQ for sample size calculations for clinical trials. Calculated sample size was 72 per group based on a 3 point difference between groups on the RDQ at day 30, assuming an alpha set at 0.05 (2 tailed), power set at 90%, and a standard deviation of 5 points. Assuming a 5% dropout rate, a minimum of 76 patients per group was required.

Statistical analysis was performed on the intention-to-treat (ITT) population, taking into account all randomized patients who received at least one dose of the study medication, and using the last observation carried forward technique. The primary criterion (RDQ score) and the VAS pain were studied by a 2-factor (time × treatment) analysis of variance on repeated measures. The chi-square test and the Wilcoxon rank test were used for qualitative variables. SAS program (version 12) was used for statistical analysis and the level of significance was defined as $p < 0.05$.

RESULTS

A total of 162 patients were enrolled. One patient who withdrew consent after randomization and did not take study medication (ATP) was excluded from the analysis. There was no significant difference between groups regarding baseline characteristics (Table 1). Poor compliance (defined as a consumption ratio of less than 80%) was recorded in 6.5% and 3.9% of the ATP and placebo groups, respectively ($p = 0.46$).

In both groups, RDQ decreased during the course of the treatment by nearly 50% of its initial value. The mean values of the RDQ dropped from 10.3 ± 2.8 (baseline) to 7.5 ± 3.8 (day 7) and 5.2 ± 5.2 (day 30) in the ATP group, and from 11.0 ± 3.5 (baseline) to 9.1 ± 4.2 (day 7) and 6.1 ± 4.3 (day 30) in the placebo group. The difference between the 2 groups was statistically significant at day 7 ($p = 0.02$) but not at day 30 ($p = 0.2$). In other words, the mean decrease was more pronounced in the ATP group (2.8 ± 3.1) than in the placebo group (2.0 ± 2.6) at day 7, with a between-group difference that approached statistical significance ($p = 0.06$). The mean decrease from baseline of RDQ was again very similar in the ATP group (5.1 ± 3.9) and the placebo group (5.0 ± 4.2) at endpoint (primary outcome). There were no statistically significant differences in the secondary outcomes between groups, except for the use of rescue analgesia, in favor of ATP ($p = 0.04$) (Table 2).

Both compounds were well tolerated. Three patients withdrew from the study because of an adverse event. The reasons for withdrawal were dyspepsia (2 patients in the ATP group) and surgery for disc herniation (1 patient in the placebo group). One case of dyspepsia was judged to be possibly drug related by the investigator.

DISCUSSION

During recent years, interest in the subacute LBP phase has increased. This phase has been conceptualized as the period

Table 1. Baseline characteristics of the study patients. Data are expressed as mean ± standard deviation, unless otherwise described.

Characteristics	ATP Group n = 81	Placebo Group n = 80	p*
Age, yrs	42.8 ± 9.9	41.0 ± 9.8	0.23
Females, %	59.3	57.5	0.82
Body mass index	25.8 ± 4.7	25.3 ± 4.9	0.48
History of LBP, %	70.4	75.0	0.50
Employed, %	74.1	77.5	0.61
On medical leave, %	4.9	11.3	0.14
Duration of symptoms, days	52 ± 15	50 ± 14	0.63
RDQ score	10.3 ± 2.8	11.0 ± 3.5	0.15
Pain, VAS, mm	59.1 ± 18.0	60.0 ± 16.9	0.74

* Statistical significance determined by Student's t test (continuous variables with normal distribution), Mann-Whitney U test (continuous variables with abnormal distribution), or chi-square test (dichotomous variables).

Table 2. Efficacy analysis at treatment endpoint (Day 30).

	ATP Group n = 81	Placebo Group n = 80	p
	Mean Difference from Baseline		
RDQ score, primary outcome	−5.1 ± 3.9	−5.0 ± 4.2	0.78
Pain, VAS, mm	−30.4 ± 23.3	−26.4 ± 25.0	0.29
Patient global assessment, %	n = 76	n = 78	0.34
Strongly improved	47.4	38.5	
Slightly improved	27.6	38.5	
Unchanged or worsened	25.0	23.0	
Physician global assessment, %	n = 76	n = 78	0.68
Strongly improved	50.0	43.6	
Slightly improved	27.6	33.3	
Unchanged or worsened	22.4	23.1	
Dextropropoxyphene-acetaminophen, number of tablets	16.2 ± 19.0	23.4 ± 24.3	0.04

during which the biopsychological impairments begin to develop for those patients who do not recover from the acute LBP phase[3,13]. Considering the proposed importance of this phase, it is worthy to note that there have been few clinical studies in patients experiencing subacute LBP.

Our study was designed to establish whether oral ATP, a drug used as an adjunct in the treatment of LBP in France, can improve symptoms in patients with subacute LBP when compared to placebo. The RDQ was our primary clinical outcome since it is one of the 2 recommended back specific measures of function, the second one being the Oswestry Disability Index (ODI)[14]. The RDQ is short, simple to complete, and readily understood by patients[12]. Its scores correlate well with other measures of physical function, including the ODI[12]. Relatively high correlations have also been found between RDQ scores and pain ratings[12]. Furthermore, a validated translation of the RDQ is available in French[11]. These characteristics, along with the evidence of the scientific validity of the RDQ, determined our choice.

This clinical trial showed that the mean decrease of RDQ was about 5 points in both ATP and placebo treated patients at endpoint. Others have suggested that the smallest change in RDQ likely to be clinically significant lies between 2.5 and 5[12]. However, this may vary, depending on patients' initial RDQ scores[15]. Stratford, *et al*[15] estimated that changes of 4 or 5 should be considered clinically important in patients with moderate disability (initial RDQ scores of 5 to 12 or 9 to 16, respectively). Accordingly, the improvement in physical function observed in our study appeared to be clinically important in both groups. Thus the efficacy of oral ATP could have been undermined by high placebo response rates. The improvement occurred somewhat faster in the ATP group than in the placebo group, the between-group difference in RDQ scores being of borderline statistical significance (p = 0.06) at day 7 although this 0.8 difference cannot be regarded as clinically important.

One of the potential benefits of this type of treatment is the possibility of reducing the intake of analgesics. We found a statistically significant difference in mean rescue analgesic use between the ATP and placebo groups.

However, the clinical relevance for this is uncertain inasmuch as the use of dextropropoxyphene and acetaminophen combination tablets was lower than expected in both groups.

Finally, oral ATP appeared to be safe. No severe drug related adverse event was recorded in patients receiving this compound; only 2 patients complained of dyspepsia.

In summary, our study suggests that oral ATP might provide some benefits in patients with subacute LBP, with an early acting effect and a lower use of rescue analgesia. However, the current evidence is insufficient to recommend this drug for people with LBP. Further studies are needed to answer the following questions: (1) What are the bioavailability and the pharmacokinetic properties of oral ATP? (2) What are its mechanisms of action in LBP? (3) What is the most effective dosage? (4) Is oral ATP useful in treating patients with LBP whatever the duration of symptoms? (5) Does oral ATP decrease the intake of all types of analgesics, including non-steroidal antiinflammatory drugs?

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