A controlled multicenter pediatric study in the treatment of acute respiratory tract diseases with the aid of a new specific compound, erdosteine (IPSE, Italian Pediatric Study Erdosteine)

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A controlled multicenter pediatric study in the treatment of acute respiratory tract diseases with the aid of a new specific compound, erdosteine (IPSE, Italian Pediatric Study Erdosteine)

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Key words erdosteine – acute bronchitis – pediatrics – comparative clinical trial

Abstract. Introduction. Erdosteine is an original drug which has been suggested as secretolytic compound and promoter of respiratory ventilation in the treatment of acute and chronic respiratory diseases. Moreover, the drug possesses also scavenging, antioxidant, and bacterial anti-adhesivity properties. From a clinical point of view the best results have been obtained by combined treatment with an antibiotic agent of useful spectrum activity. Aim of the present study was to evaluate the improvement induced in the risk/benefit ratio by erdosteine on the broad-spectrum antibiotic (ampicillin) in the treatment of acute lower respiratory tract diseases in the pediatric field. Material and methods. A controlled multicenter double-blind parallel group trial was planned comparing erdosteine, supplied as syrup 3.5% or as sachets 225 mg, versus the relevant placebo. The tested compounds were administered in association with ampicillin. Two-hundred (n = 200) subjects entered the trial, randomly selected among patients monitored by the different centers, and were assigned to one of the treatments under evaluation, i.e. active compound or placebo with the aim to constitute two comparative homogeneous groups of 100 subjects each. Subsequently each group was again divided according to age in two equivalent subgroups of 50 patients each and treated with the syrup 3.5% (age from 2 to 4 years) or the sachet form (age from 5 to 10 years). The treatments administered in the two comparison groups were erdosteine (syrup 3.5% and 225 mg sachets) or the relevant placebo. The erdosteine posologies were adapted according to age. The lower dosage of the 5–10 years range in comparison with the 2–4 years range was established on the base of bioavailability characteristcises of the two pharmaceutical forms. In all groups ampicillin was administered at the dosage of 100 mg/kg/day, according to a b.i.d. time schedule. The primary efficacy criterion was the cough score evaluated in a subjective way and expressed with the following scores: 1 = absent; 2 = mild; 3 = moderate; 4 = severe. The secondary efficacy end-points were: body temperature (expressed in °C); the polypnea, rhonchi and rales estimation with a rating scale similar to that previously mentioned. These parameters were determined before starting of the treatment (V0); at the 3rd ± 1 (V1) and at the 7th ± 2 (V2) day of treatment. The body temperature was measured orally in the morning at awakening time with a mercury thermometer. Obtained data expressed in Celsius degrees are recorded by the investigator in the patient file during control visits. The safety of adopted treatments was evaluated with two different approaches. The clinical part was determined with the adverse drug reactions (ADRs) estimate. The biological safety was estimated at admission day (day 0) and at the final visit by means of a sophisticated statistical approach. Results. The final results were the following: Erdosteine syrup 3.5%; concerning cough (primary end-point) in the group of patients (n = 50) treated with erdosteine it has been possible to point out a reduction of 23.8% at V1, i.e. after 3 ± 1 days, and of 59.8% at V2, i.e. after 7 ± 2 days. In the group of patients treated with placebo (n = 50) the reduction has been of 20.1% at V1 and of 36.6% at V2. The statistical analysis evidenced p values < 0.01 for times, treatments, time × treatments. The relevant results are summarized in Table 2. Erdosteine sachets 225 mg: concerning cough (primary end-point) in the group of patients (n = 50) treated with erdosteine it has
been possible to point out a reduction of 17.6% at V1, i.e. after 3 ± 1 days, and of 56.8% at V2, i.e. after 7 ± 2 days. In the group of patients treated with placebo (n = 50) the reduction has been of 15.6% at V1 and of 31.8% at V2. The statistical analysis evidenced p values < 0.01 for times, treatments, time × treatments. **Conclusions:** In general terms, it could be concluded that erdosteine, administered in association with an antibiotic in pediatric febrile lower respiratory tract infections is quite useful, allowing a more rapid and definite amelioration of the clinical evidence, with reduction of the relevant symptomatology (cough, body temperature, ronchi, rales). The safety and tolerability of the treatment has been proved to be as good as already known from the existing documentation on the product.

**Introduction**

Erdosteine is an original drug which has been suggested as secretolytic compound and promoter of respiratory ventilation in the treatment of acute and chronic respiratory diseases [Olivieri et al. 1991]. Moreover, the drug possesses also scavenging, anti-oxidant, and bacterial anti-adhesivity properties [Biagi et al. 1989, Braga et al. 1999, Gazzani et al. 1989].

From a clinical point of view the best results have been obtained by combined treatment with an antibiotic agent of useful spectrum activity [Marchioni 1995].

**Subjects, materials and methods**

Aim of the present study was to evaluate the improvement induced in the risk/benefit ratio by erdosteine on a broad-spectrum antibiotic (ampicillin) in the treatment of acute lower respiratory tract diseases in the pediatric field. Therefore, a controlled multicenter double-blind, parallel groups trial has been planned comparing erdosteine, supplied as syrup 3.5% or as sachets 225 mg, versus the relevant placebo. The tested compounds were administered always in association with ampicillin. The investigators agreed to perform the trial strictly according to the principles of the Helsinki Declaration (last amendment). Moreover, the study protocol has been approved by the Ethics Committee of all involved centers. An informed consent was obtained before study inclusion from the patients parents after an exhaustive explanation of study purposes and procedures. Two-hundred (n = 200) subjects entered the trial, randomly selected among patients monitored by the different centers, and were assigned to one of the treatments under evaluation, i.e. active compound or placebo with the aim to constitute two comparative homogeneous groups of 100 subjects each. Subsequently each group was again divided according to age in two equivalent subgroups of 50 patients each and treated with the syrup 3.5% (age from 2 to 4 years) or the sachet form (age from 5 to 10 years).

Inclusion criteria were: clinical diagnosis of acute lower respiratory tract disease (i.e. acute bronchitis, bronchoalveolitis etc.) without evidence of acute parenchymal or pleuric involvement.

Exclusion criteria were: history of hypersensitivity to drugs of the same pharmaceutical class, like thiol derivatives, penicillins, cephalosporins; severe concomitant systemic disease; recent therapy (i.e. within 7 days before the start of treatment with erdosteine) with mucolytics, NSAIDs, cough suppressants, antibacterial agents, bronchodilators, steroids.

The treatments administered in the two comparison groups were erdosteine (syrup 3.5% and 225 mg sachets) or the relevant placebo. The erdosteine posologies were adapted according to age. Therefore, for the syrup 3.5% (n = 50 patients) the following posologies were adopted: age 2 – 3 years: 2 x 2.5 ml/day (i.e. 175 mg/day) b.i.d., morning and evening; age 3 – 4 years: 2 x 5 ml/day (i.e. 350 mg/day) idem. For the sachets the adopted dosages were: age 5 – 6 years: 1 sachet/day (i.e. 225 mg/day), age 6 – 10 years: 2 sachets/day (i.e. 450 mg/day).

The lower dosage of the 5 – 6 years range in comparison with the 3 – 4 years range was established on the base of bioavailability characteristics of the two pharmaceutical forms.

In all groups ampicillin was administered at the dosage of 100 mg/kg/day, according to a b.i.d. time schedule.
To assure the double-blind conditions, the pharmaceutical forms of erdosteine and placebo were absolutely indistinguishable (smell, taste, color). The random allocation schedule was obtained with a computer-specific program based on the casual number series.

Concerning concomitant treatments, mucolytics, NSAIDs, cough suppressants, antibacterial agents, bronchodilators and steroids had to be avoided during the last week preceding the trial period. Apart from the ampicillin administered to all participants the following therapies have been used: paracetamol syrup or suppositories 250 mg: in 96 subjects; theophylline suspension: in 5 cases; salbutamol 2 mg tablets: in 16 cases.

The cases treated with theophylline and salbutamol have been maintained in the statistical evaluation of the compound due to the fact that their administration has to be done not in a continuous way, but only in case of necessity, i.e. 2 – 3 times in all the treatment periods.

The primary efficacy criterion was the cough score evaluated by the investigators in a subjective way and expressed with the following scores: 1 = absent; 2 = mild; 3 = moderate; 4 = severe.

The secondary efficacy end-points were: body temperature (expressed in ° C); polypnea, ronchi and rales estimation using a rating scale similar to that of cough measurement, previously mentioned.

These parameters were determined before starting of the treatment (V0); at the 3rd ± 1 (V1) and at the 7th ± 2 (V2) days of treatment. Body temperature was measured orally in the morning at awakening time with a mercury thermometer. Obtained data expressed in Celsius degrees are recorded by the investigator in the patient file during control visits.

Safety of adopted treatments was evaluated with two different approaches.

The clinical part was determined with adverse drug reaction (ADR) estimate. To this aim the patient (or his/her representative, parent, nurse etc.) was asked at visit times (days 3 and 7) to report any ADR experienced, giving an evaluation of intensity and duration. The investigator recorded the reported ADRs, together with reactions directly observed at visit time, in the individual patient's file. During the recording of the ADRs the investiga-
Table 1. Overall comparability of treatment groups

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Statistical test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Chi-square</td>
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<td>Age</td>
<td>T-test</td>
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1: concomitant treatments

Table 2. Primary end point (cough score) results

<table>
<thead>
<tr>
<th>Erdosteine</th>
<th>V0</th>
<th>V1</th>
<th>V2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.3</td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td>± SD</td>
<td>0.57</td>
<td>0.58</td>
<td>0.47</td>
</tr>
<tr>
<td>% change to V0</td>
<td>28.60</td>
<td>59.80</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.4</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>± SD</td>
<td>0.53</td>
<td>0.65</td>
<td>0.74</td>
</tr>
<tr>
<td>% change to V0</td>
<td>28.10</td>
<td>58.60</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Overall comparability of treatment groups

<table>
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<th>ITEM</th>
<th>Statistical test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Age</td>
<td>T-test</td>
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<tr>
<td>Height</td>
<td>T-test</td>
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<tr>
<td>Weight</td>
<td>T-test</td>
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</tr>
<tr>
<td>CONCOE</td>
<td>Chi-square</td>
<td>0.64</td>
</tr>
</tbody>
</table>

1: concomitant treatments

Table 4. Primary end point (cough score) results

<table>
<thead>
<tr>
<th>Erdosteine</th>
<th>V0</th>
<th>V1</th>
<th>V2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.0</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>± SD</td>
<td>0.45</td>
<td>0.54</td>
<td>0.45</td>
</tr>
<tr>
<td>% change to V0</td>
<td>-17.60</td>
<td>-56.60</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.1</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>± SD</td>
<td>0.40</td>
<td>0.53</td>
<td>0.65</td>
</tr>
<tr>
<td>% change to V0</td>
<td>-15.08</td>
<td>-31.80</td>
<td></td>
</tr>
</tbody>
</table>

been utilized (LSM) with the Catmod procedure, with the aim to consider all-together the different sources of variation. A Wilcoxon test was performed at the different times of examination. The laboratory was evaluated according to the following procedure: 1st step: ANCOVA, according to a factorial model, with the basal value as covariant variable; 2nd step: the obtained values were compared with the normal laboratory range. The conditions of subjects at V0 and at V2 were compared. The relative changes were estimated and then a binomial test with p = q = 0.5 was performed.

Results

Erdosteine syrup 3.5%

A total number of 100 inpatients, of mean age (± SD) 2.97 ± 0.83 years and with male/female ratio 53/47 were enrolled, all with diagnosis of acute respiratory tract diseases (acute bronchitis, asthmatic bronchitis, tracheo-bronchitis, bronchoalveolitis). This sample population was randomly divided in two comparable groups.

The first group of 50 subjects of mean age (± SD) 2.86 ± 0.83 years and male/female ratio 31/19, was treated according to the regimen A, i.e. erdosteine plus ampicillin, for a period of 6.80 ± 0.53 days (range 6 - 8 days). No drop-outs have been observed at the end of the experimental part. The second group of 50 subjects of mean age (± SD) 3.83 ± 0.83 years and male/female ratio 22/28, was treated according to the regimen B, i.e. placebo plus ampicillin, for a period of 6.84 ± 0.72 days (range 5 - 9 days). One drop-out was observed at the end of the experimental part: it was due to the poor efficacy of the treatment.

The homogeneity of basal conditions was tested with Chi-square and t-test. No statistically significant differences were observed.

The daily dose of erdosteine, i.e mg 175/day in 30 subjects and mg 350/day in 20, was administered for a mean duration (± SD) of 6.80 ± 0.53 days.

Treatment groups were compared for all critical measures of effectiveness (primary and secondary end-points).

Concerning cough (primary end-point) in the group of patients (n = 50) treated with erdosteine it was possible to point out a reduction of 23.8% at V1, i.e. after 3 ± 1 days, and of 59.8% at V2, i.e. after 7 ± 2 days. In the group of patients treated with placebo (n = 50)
the reduction was of 20.1% at V1 and of 36.6% at V2. The statistical analysis evidenced p values < 0.01 for times, treatments, time x treatments. The relevant results are summarized in Table 2.

Concerning the secondary criteria (body temperature, polyneea, rhonchi, rales) the following results were obtained:

body temperature: with erdosteine a reduction of 3.6% was observed at V1 and of 5.6% at V2; with placebo the corresponding values were –2.8% at V1 and –4.6% at V2. Statistical significance for time, time x treatments and centers.

Polyneea: with erdosteine a reduction of 35.2% was observed at V1 and of 49.5% at V2; with placebo the corresponding values were –29.2% at V1 and –38.4% at V2. Statistical significance only for time.

Rhonchi: with erdosteine a reduction of 33.3% has been observed at V1 and of 59.7% at V2; with placebo the corresponding values were –24.4% at V1 and –41.1% at V2. Statistical significance for time and time x treatments.

Rales: with erdosteine a reduction of 17.6% has been observed at V1 and of 56.3% at V2; with placebo the corresponding values were –14% at V1 and –31.2% at V2. Statistical significance for time, time x treatments and centers.

Regarding the tolerability, one case of cutaneous rash was observed with erdosteine, but of short duration, mild evidence and with no influence on treatment realization. As far as the laboratory variables are concerned in the first step, the ANCOVA test has been performed (basal values as covariate) evidencing a significative difference (p < 0.01) only for red cells, but with no clinical relevance considering the means. In the second step the binomial test p = q = 0.5 was performed where it had been pointed out that the subjects modify their status only for variables: white cells, ESR, mucoproteins and C-reactive protein. This modification is homogeneous for erdosteine and placebo, without significance for difference between treatments.

**Erdosteine sachets 225 mg**

Hundred (n = 100) in-patients, of mean age (± SD) 6.68 ± 1.69 years and with male/female ratio 56/44 were enrolled. The general diagnosis was acute respiratory tract disease (acute bronchitis, asthmatic bronchitis, tracheo-bronchitis, bronchialveolitis). Again this sample population was randomly divided in two comparable groups.

The first group of 50 subjects of mean age (± SD) 6.86 ± 1.48 years and male/female ratio 28/22, was treated according to the regimen A, i.e. erdosteine plus ampicillin, for a period of 6.88 ± 0.59 days (range 6 – 9 days). The second group always of 50 subjects of mean age (± SD) 6.50 ± 1.87 years and male/female ratio 28/22, was treated according to the regimen B, i.e. placebo plus ampicillin, for a period of 6.80 ± 0.67 days (range 5 – 9 days). No drop-outs were observed at the end of the experimental part.

Also, in this case the homogeneity of the basal conditions was tested with Chi-square and t-test. No statistically significant differences were observed.

The daily dose of erdosteine, i.e mg 225/day in 16 subjects and mg 450/day in 34, was administered for a mean duration (± SD) of 6.88 ± 0.59 days.

Treatment groups have been compared for all critical measures of effectiveness (primary and secondary end-points).

Concerning cough (primary end-point) in the group of patients (n = 50) treated with erdosteine could be observed a reduction of 17.6% at V1, i.e. after 3 ± 1 days, and of 56.8% at V2, i.e. after 7 ± 2 days. In the group of patients treated with placebo (n = 50) the reduction has been of 15.6% at V1 and of 31.8% at V2. The statistical analysis evidenced p values < 0.01 for times, treatments, time x treatments. The relevant results are summarized in Table 4.

Concerning the secondary criteria (body temperature, polyneea, rhonchi, rales) the following results were obtained:

body temperature: with erdosteine a reduction of 3.3% was observed at V1 and of 4.6% at V2; with placebo the corresponding values were –2.9% at V1 and –4.4% at V2. Statistical significance for time and centers.

Polyneea: with erdosteine a reduction of 25.0% was observed at V1 and of 32.9% at V2; with placebo the corresponding values were –25.6% at V1 and –37.2% at V2. Statistical significance only for time.
Rhonchi: with erdosteine a reduction of 38.6% was observed at V1 and of 49.5% at V2; with placebo the corresponding values were −20.6% at V1 and −41.1% at V2. Statistical significance for time, centers and time × treatments.

Rales: with erdosteine a reduction of 17.7% was observed at V1 and of 47.8% at V2; with placebo the corresponding values were −11.7% at V1 and −23.3% at V2. Statistical significance for time, time × treatments and centers.

Regarding the tolerability no one case of adverse reaction was observed with erdosteine. As far as the laboratory variables are concerned in the first step the ANCOVA test was performed (basal values as covariate) evidencing a significant difference (p < 0.01) only for AST and ALT, but with no clinical relevance according to the means. In the second step the binomial test p = q = 0.5 was performed where it has been pointed out that the subjects modify their status only for variables: white cells, ESR, mucoproteins and C-reactive protein. This modification is homogeneous for erdosteine and placebo, without meaning therefore in terms of difference between treatments.

**Discussion**

The results of the present double-blind study could be commented in the following way, divided per pharmaceutical form.

**Erdosteine syrup 3.5%**

The already well-known [Titi 1991] therapeutic activity of erdosteine in the treatment of pediatric lower respiratory tract diseases with a reduction of the cough scores of 57% after 7 days of treatment was confirmed. Comparatively, the reduction with placebo on the same parameter was 32%. This difference was highly statistically significant.

To be underlined is that the comparative evaluation of basal values evidenced the homogeneity of background conditions.

Only one adverse reaction was observed and also biological safety was ensured.

**Erdosteine sachets 225 mg**

The reduction of cough scores was 60% after 7 days of treatment, comparatively the reduction with placebo on the same parameter 37%. This difference was highly statistically significative.

Also, in this case is to be underlined that the comparative evaluation of basal values evidenced the homogeneity of background conditions.

No important adverse reactions have been observed and also the biological safety was ensured.

**Conclusions**

In general terms it can be concluded that erdosteine, administered in association with an antibiotic in pediatric febrile lower respiratory tract infections is quite useful, allowing a more rapid and definite amelioration of the clinical evidence, with reduction of the relevant symptomatology (cough, body temperature, rhonchi, rales).

Safety and tolerability of the treatment has shown to be as good as already known from the existing documentation on the product.

**References**


Titi O et al 1991 Pharmacokinetics of erdosteine and erythromycin stinoprate when administered alone or in combination to children affected by acute tracheobronchitis. Med Prax 12: 143