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# Bronchodilatory effect of inhaled zardaverine, a phosphodiesterase III and IV inhibitor, in patients with asthma

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**ABSTRACT: Zardaverine is a newly developed selective phosphodiesterase III and IV inhibitor. This study investigates the bronchodilatory properties of zardaverine, administered by inhalation.**

**Twelve patients with reversible bronchial obstruction (increase in forced expiratory volume in one second (change $FEV_1$ % predicted) at least 15% after 200 μg salbutamol, median age 31 yrs, range 21–54 years) entered the double-blind, crossover study. Four puffs of either zardaverine (total dose 6 mg) or placebo were inhaled at 15 min intervals. Pulmonary function (specific airway conductance (sGaw) and $FEV_1$ was measured by body plethysmography at regular intervals (5 and 12 min after each puff and, in addition, 30, 60, 120, 180 and 240 min after the last puff).**

**Compared to placebo, sGaw and $FEV_1$ increased significantly during the first hour of repeated inhalations, but not during the entire observation period of almost 5 h. The maximum mean difference between zardaverine and placebo for $FEV_1$ was 0.3 *l* or 12% and occurred approximately 1 h after inhalation of the first puff. In seven patients $FEV_1$ increased by >15%. The duration of action varied considerably between patients. Three patients complained of side-effects (headache, drowsiness, vertigo, nausea), and one of these dropped out of the study due to vomiting.**

**We conclude that inhalational administration of zardaverine has a modest and short-lasting bronchodilating activity.**

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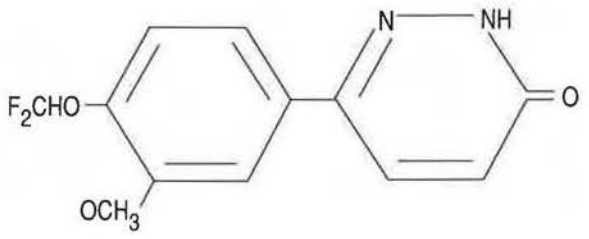
Bronchial asthma is characterized by increased airway resistance, induced to various degrees by elevated bronchomotor tone, inflammation, mucosal oedema and viscous hypersecretion. The contraction of bronchial smooth muscle depends to a great extent on intracellular $Ca^{++}$ levels and cyclic adenosine monophosphate (cAMP) content. Increase in intracellular cAMP concentration induces smooth muscle relaxation.




6-(4-difluormethoxy-3-methoxyphenyl)-3 [2H] pyridazinone

Fig. 1. – Chemical structure of zardaverine.

The key enzyme catalysing the breakdown of cAMP is phosphodiesterase (PDE). There are several isotypes of PDE that differ in substrate specificity and tissue distribution [1, 2]. The newly developed PDE inhibitor, zardaverine, (Byk Gulden Pharmaceuticals, Germany) (fig. 1), selectively inhibits type III/IV PDE (cAMP specific) [3]. Animal experiments suggest that zardaverine exhibits bronchodilatory and anti-inflammatory properties [3, 4]. In particular, it was shown in guinea-pigs that zardavarine inhibits the release of inflammatory mediators and the infiltration of the lung by pro-inflammatory cells [4].

The present study is the first investigation into the acute bronchodilatory effects of inhaled zardavarine in patients presenting with asthma.

## Patients and methods

The twelve patients (3 female), age 21–54 yrs, median 31 yrs, had mild to moderate reversible bronchial obstruction (forced expiratory volume in one second ($FEV_1$) median 56% (of predicted (range 50–85%)).

Their increase in $FEV_1$ (% predicted) was at least 15% after inhalation of 200 μg salbutamol (median 25%, range 15–36%). Patients entered the study after having given written informed consent. Individual patient characteristics are given in table 1. The study was performed in accordance with the principles of the Declaration of Helsinki in its revised versions of Tokyo (1975) and Venice (1983). The trial protocol was scrutinized by an independent Ethics Committee ("Freiburger Ethik Kommission").

At the first visit, a routine pulmonary function test (constant-volume, pressure-compensated body plethysmography and spirometry (Jäger Masterlab, Würzburg, Germany)) and a test for reversibility of bronchial obstruction after inhalation of 200 μg salbutamol were performed. Electrocardiography (ECG) and routine laboratory work-up were carried out. On a second and third visit (with one week interval), zardaverine or placebo was given to each patient, at approximately the same time of day, in a double-blind, randomized, crossover fashion. On both study days, baseline pulmonary function was recorded. The patients then inhaled four puffs of the study medication from a metered-dose inhaler, delivering either zardaverine (1.5 $mg \cdot puff^{-1}$) or placebo. Inhalation of the single puffs was separated by 15 min intervals. Five minutes after each inhalation specific airway conductance (sGaw) and airway resistance (Raw) were recorded. Twelve minutes after each puff, and, additionally, 30, 60, 120, 180 and 240 min after the fourth puff sGaw, Raw, $FEV_1$ and maximal expiratory flow at 25 and 75% forced vital capacity ($MEF_{25}$ and $MEF_{75}$) were determined.

All patients were in a stable clinical status. Inhaled $\beta_2$-agonists were permitted up to 8 h prior to inhalation of the study medication and further allowed when needed. Additionally, four patients received inhaled steroids (maximum 200 μg beclomethasone as a regular daily dose). No other anti-asthmatic drugs were used. Smokers (n=5) were not allowed to smoke during the study.

## Statistical analysis

The primary parameter for confirmative statistical analysis was sGaw. The sample size of 12 patients was sufficient to detect, with a power of 80%, differences in the magnitude of 90% of one standard deviation as significant at the 5% level (two-sided) [5].

$FEV_1$, $MEF_{25}$ and $MEF_{75}$ were considered secondary parameters and statistically analysed with an explorative intention. Values of Raw were not considered since Raw and sGaw are essentially only different calculations of the same phenomenon.

The distribution-free crossover analysis [6] was used to test for the homogeneity of the baseline values and for differences between zardavarine and placebo. In addition to the time average during the entire study period of almost 5 h, the time average during the first hour, *i.e.* up to 12 min after the fourth inhalation, was considered. Time averages provide a robust measure of the response during the respective time interval. They were calculated on an individual basis by the trapezoidal formula and then subjected to the statistical analysis.

## Results

Efficacy data are reported on the 11 patients who completed the trial. Baseline readings of sGaw, $FEV_1$, $MEF_{25}$ and $MEF_{75}$ were comparable at both visits; there were no carry-over or period effects.

For sGaw, the difference between the mean values of zardaverine and placebo had its maximum of 0.23 $kPa^{-1} \cdot s^{-1}$ 5 min after the third inhalation (fig. 2). A 40% increase in sGaw compared to placebo, which was considered to be clinically relevant, was observed in 8 of the 11 patients. In four patients it lasted less than 1 h, whilst in the other four it lasted 3.5–4.5 h, *i.e.* during practically the entire observation period.

Table 1. – Demographic characteristics of patients enroled in the study

| Pt no. | Sex | Smoker | Age yrs | Weight kg | Height cm | $FEV_1$ *l* | $FEV_1$ % pred | % increase in $FEV_1$ (% pred) after salbutamol | Treatment sequence |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | S | 52 | 104 | 183 | 3.1 | 79 | 32 | PZ |
| 2 | M | | 51 | 93 | 181 | 1.9 | 50 | 26 | ZP |
| 3 | M | | 32 | 70 | 183 | 3.4 | 75 | 36 | ZP |
| 4 | M | S | 21 | 84 | 184 | 2.4 | 52 | 26 | ZP |
| 5 | F | | 54 | 55 | 152 | 1.5 | 71 | 24 | PZ |
| 6 | M | S | 25 | 72 | 174 | 2.3 | 54 | 17 | ZP |
| 7 | M | | 29 | 66 | 168 | 2.9 | 74 | 23 | ZP |
| 8 | M | | 45 | 82 | 182 | 2.0 | 50 | 25 | PZ |
| 9 | F | S | 23 | 51 | 164 | 1.9 | 50 | 15 | PZ |
| 10 | M | | 29 | 72 | 185 | 2.6 | 56 | 24 | ZP |
| 11 d | F | | 29 | 58 | 171 | 2.9 | 85 | 33 | ZP |
| 12 | M | S | 48 | 87 | 176 | 2.7 | 72 | 15 | PZ |

d: drop-out in first treatment period; M: male; F: female; S: smoker; Z: zardaverine; P: placebo; $FEV_1$: forced expiratory volume in one second.

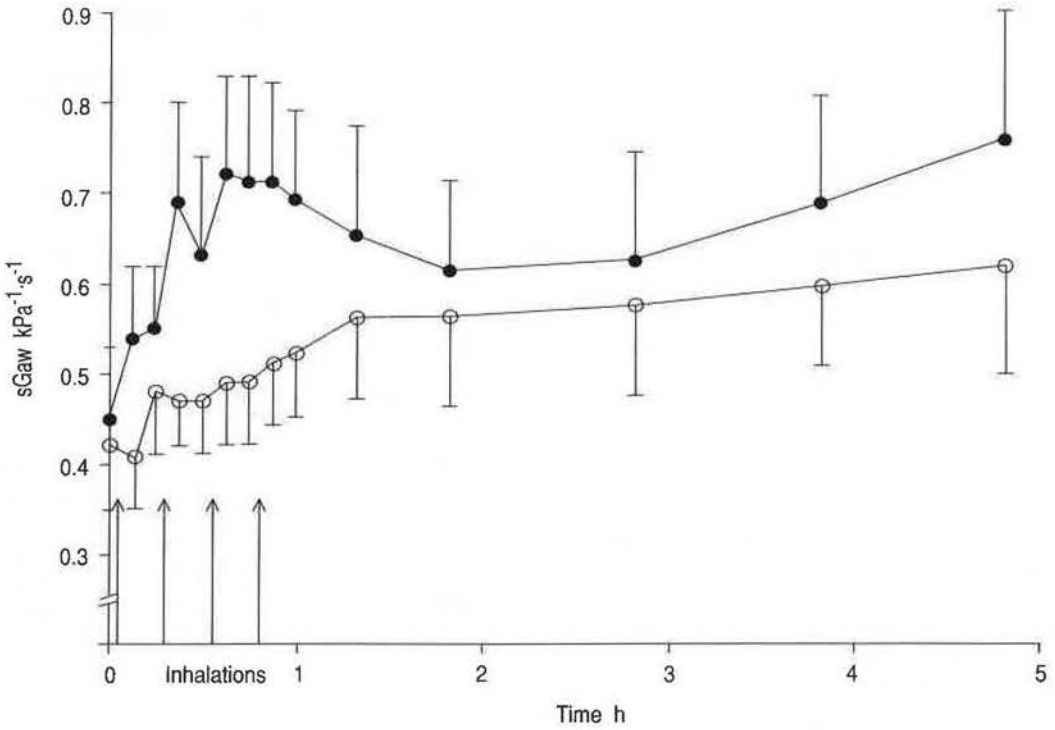



Fig 2. – Effect of inhaled zardaverine (●) on sGaw compared to placebo (○) (mean, SEM), in 11 subjects. Total dose of zardaverine was 6 mg. sGaw: specific airway conductance. Note that the vertical axis does not extend to zero.

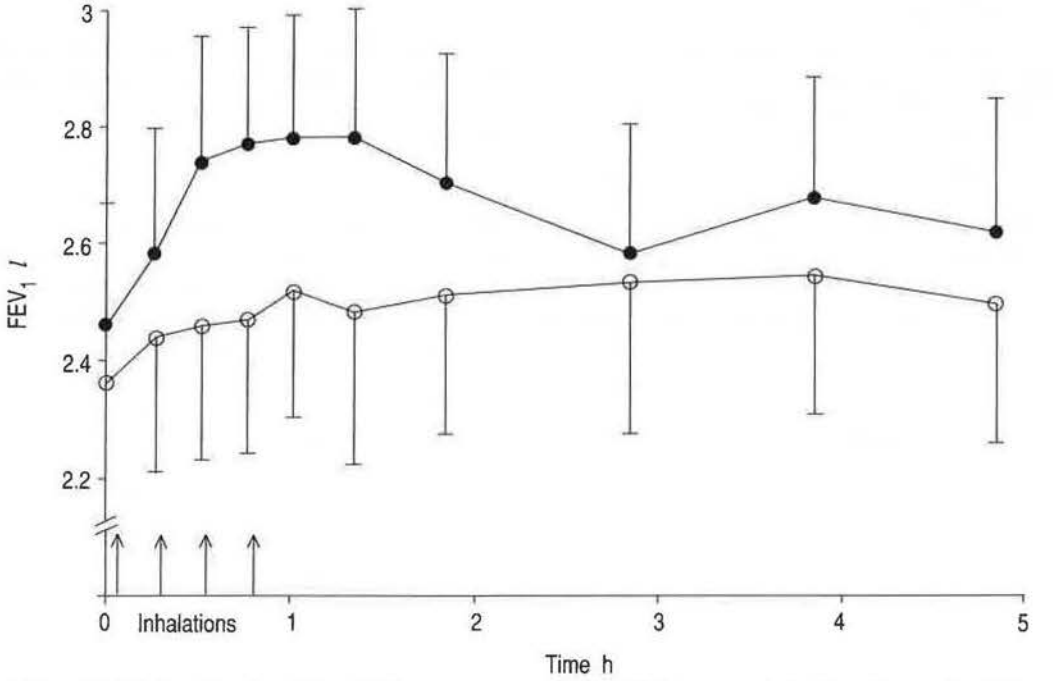



Fig. 3. – Effect of inhaled zardaverine (●) on $FEV_1$ compared to placebo (○) (mean, SEM), in 11 subjects. Total dose of zardaverine was 6 mg. $FEV_1$: forced expiratory volume in one second. Note that the vertical axis does not extend to zero.

This is reflected in a significant ($p<0.01$) increase of 36% from 0.47±0.21 kPa$^{-1}$·s$^{-1}$ (placebo) to 0.64±0.31 kPa$^{-1}$·s$^{-1}$ (zardaverine) during the first hour of observation. The increase during the 5 h observation period was 18% and statistically nonsignificant.

The maximum difference between the $FEV_1$ means was observed 12 min after inhalation of the third puff and amounted to 0.3 *l* or 12% (fig. 3). It is, thus, less than the 15% increase in $FEV_1$ after two puffs of salbutamol considered in the initial reversibility test. In seven out of 11 patients the maximum increase in $FEV_1$ was at least 15%. The time-averaged $FEV_1$ values during the first hour of repeated inhalations increased by 9% from 2.46±0.73 to 2.68±0.70 *l* ($p<0.05$).

The increase during the 5 h observation period amounted to 8% and was statistically nonsignificant.

No additional information was gained from $MEF_{75}$ and $MEF_{25}$ measurements.

Three patients, all female, complained of adverse effects (table 2). One patient had to be withdrawn from the trial due to repeated vomiting after inhalation of the fourth puff of zardaverine. No side-effects were reported on placebo days.

Table 2. – Adverse events after inhalation of zardaverine (total dose 6 mg)

| Pt no. | Age yrs | Adverse reaction | Duration | Severity |
|---|---|---|---|---|
| 5 | 54 | Headache | 2 h | Moderate |
| | | Drowsiness ("like being drunk") | 2 h | Moderate |
| | | Restlessness | 2 h | Moderate |
| 9 | 23 | Vertigo | 2 h | Moderate |
| | | Nausea | 2 h | Moderate |
| | | Numb sensation of tongue | 2 min | Mild |
| 11 d | 29 | Nausea | 45 min | Moderate |
| | | Repeated vomiting | | Severe |

d: drop-out in first treatment period.

## Discussion

In this first clinical study, zardaverine significantly improved pulmonary function (sGaw, $FEV_1$ and $MEF_{75}$) during the first hour of repeated inhalations but not during the entire observation period of almost 5 h. The overall duration of bronchodilation after acute administration was rather short and varied considerably between individual patients. The reasons for this variation will have to be further investigated. Patient characteristics and other parameters such as small airway disease gave no hints as to why some of the patients responded and others did not.

The administration of four puffs at 15 min intervals makes it difficult to distinguish exactly between dose and time effects. The greatest changes in pulmonary function were observed after the first two puffs, whilst the third and fourth puffs may have prolonged this effect. Five and 12 min values of sGaw hardly differed. Thus, it may well be that the maximum effect occurs within a few minutes after inhalation.

We conclude that inhaled zardaverine has a modest and short-lasting bronchodilatory activity.

## References

1. Beavo JA. – Multiple isoenzymes of cyclic nucleotide phosphodiesterases. *Adv Second Messengers and Phosphoprotein Res*, 1988; 22: 1–38.
2. Beavo JA, Reifsnyder DH. – Preliminary sequence if cyclic nucleotide phosphodiesterase isoenzymes and the design of selective inhibitors. *Trends Pharmacol Sci*, 1990; 11: 150–155.
3. Kilian U, Beume R, Eltze M, Schudt C. – Is phosphodiesterase inhibition a relevant bronchospasmolytic principle? *In*: Agents and Actions. Suppl. 28. Intrinsic Asthma. Basel, Birkhäuser Verlag, pp. 331–348.
4. Schudt C, Beume R, Wolf H, Kilian U. – Inhibition of idiopathic and allergic lung eosinophilia in guinea-pigs by dexamethasone and zardavarine. *Schweiz Med Wschr*, 1991; 121 (Suppl. 40/II): 8.
5. Ostle B. – Statistics in Research. The Iowa State University Press, 1966.
6. Koch GG. – The use of non-parametric methods in the statistical analysis of the two-period crossover design. *Biometrics*, 1972; 28: 577–584.