

The pharmacologic and clinical properties of Oxis[®] (formoterol) Turbuhaler[®]

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Formoterol was first described as a conventional short-acting β_2 -adrenergic agonist in 1976 and was launched as an oral formulation in Japan in 1986 (1). However, Löfdahl & Svedmyr (2) discovered that an inhaled dose of 6 μ g formoterol produced bronchodilatation for at least 8 h. Hence, comprehensive, preclinical, pharmacokinetic, and clinical research at Ciba Geigy and Astra has led to the development of formoterol for inhalation. Oxis[®] Turbuhaler[®] is the formoterol product from Astra Pharmaceuticals. This combines formoterol with the highly efficient, inhalation delivery device, Turbuhaler (3). Clinical studies have shown that Oxis Turbuhaler (4.5- or 9- μ g delivered doses of formoterol, corresponding to 6- or 12- μ g metered doses, respectively) is effective. This review will detail some of the studies that have been performed in order to gain European approval for the launch of Oxis Turbuhaler. All clinical studies reported here use metered doses.

Dose-ranging studies

Single-dose, controlled studies in adults with chronic, reversible obstructive airway disease were performed to document the lowest effective dose (and possible additional effects with higher doses) of Oxis Turbuhaler.

Ringdal et al. (4) performed a double-blind, randomized, crossover study in 31 patients with a mean baseline FEV₁ of 2 l and a mean reversibility of 31%. Most of these patients were already on inhaled corticosteroids. Four doses of Oxis Turbuhaler 6, 12, 24, and 48 μ g were administered, and the mean effect on FEV₁ (primary variable), the maximum effect on FEV₁, and the remaining effect 12 h after dosing were determined and compared with the placebo response (Fig. 1). Oxis Turbuhaler increased the mean FEV₁ in a dose-dependent manner, and the maximum response was significantly different from placebo at all four doses. The mean effect over 12 h on FEV₁ and the

remaining effect 12 h after dosing were also significantly different from placebo values. The maximum effects with 24 and 48 μ g Oxis Turbuhaler on FEV₁ were not statistically different, and this may represent the top of the dose-response curve. Moreover, a dose-response relationship was also found in increase from baseline in specific airway conductance (*sGaw*) soon after inhalation. More than a 50% increase from baseline in *sGaw* was measured 1 min after inhalation of Oxis Turbuhaler at 6, 12, 24, and 48 μ g in 17, 42, 61, and 92% of the patients, respectively. Four minutes after inhalation, the corresponding values were 57, 67, 87, and 96%.

A second, double-blind, randomized, crossover dose-response study was performed by Lötvall et al. (5), comparing three doses of Oxis Turbuhaler (6, 12, and 24 μ g) with 50 μ g of salmeterol administered via Diskhaler[®]. The study included 28 patients with chronic reversible obstructive airway disease, and the mean increase in FEV₁ was determined over a 12-h period. Statistically significant dose-response relationships were noted for mean, maximum, and 12-h improvements in FEV₁. All three doses were statistically different from placebo. Oxis Turbuhaler at 24 μ g caused significantly more bronchodilatation when compared with salmeterol at 50 μ g and had a longer duration of action (Fig. 2). In addition, a dose of Oxis Turbuhaler of between 6 and 12 μ g was estimated, by interpolation, to be equipotent in bronchodilatation to salmeterol at 50 μ g. This response varied among individual patients, but Oxis Turbuhaler at 24 μ g was significantly more effective than salmeterol at 50 μ g in all cases (12-h average FEV₁). The onset of action for Oxis Turbuhaler was significantly faster for all doses when compared with salmeterol at 50 μ g, as determined by increase in FEV₁ 3 min after inhalation (Fig. 3).

In summary, these studies determined that Oxis Turbuhaler was an effective and rapid treatment (4, 5). All doses resulted in statistically significant increases in mean FEV₁ when compared with

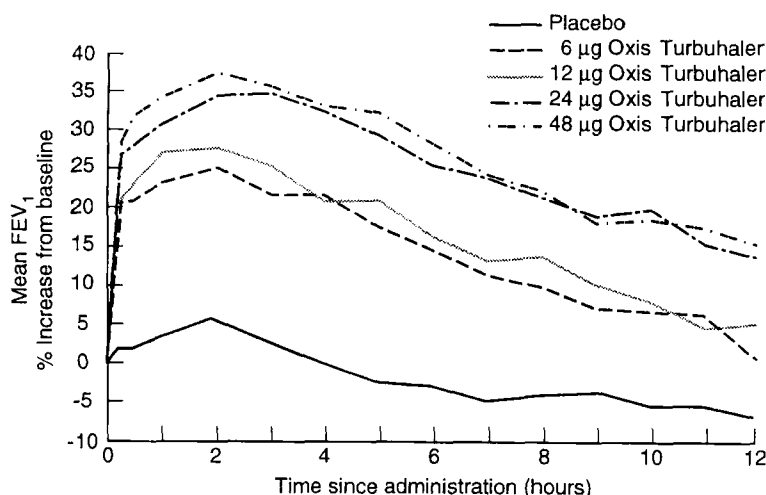


Fig. 1. Increase in FEV₁ after single doses of formoterol administered by Turbuhaler (4).

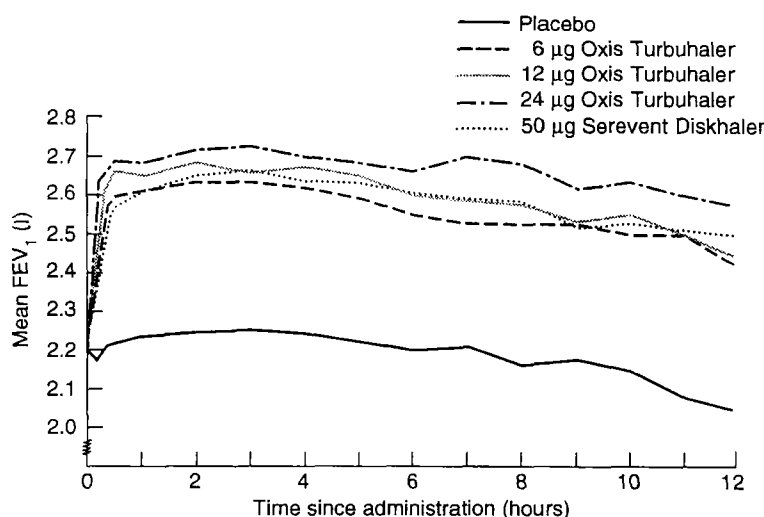


Fig. 2. Increase in FEV₁ after single doses of formoterol compared with salmeterol (5).

placebo, and this response was maintained over 12 h. The 6-, 12-, and 24-µg doses of Oxis Turbuhaler have all been approved for use in Europe.

Multiple-dose studies

A double-blind, randomized, parallel-group study, comparing three doses of Oxis Turbuhaler (6, 12, and 24 µg), was performed over a period of 4 weeks (6). A total of 221 adults with moderate asthma (90% on inhaled corticosteroids) were given Oxis Turbuhaler b.i.d., and the mean morning and evening PEF was determined over time. The immediate bronchodilating effect of Oxis Turbuhaler (15 min after inhalation) was increased significantly with all three doses when compared with placebo. The response was normally in the range of 40–45 l/min and was similar with all three doses. This

improvement was seen after the first application of study medication and was maintained at this level throughout the study. Furthermore, all doses of Oxis Turbuhaler were significantly more effective than placebo, with respect to PEF, 12 h after the last intake (Fig. 4), and improvements in asthma symptoms and reductions in night-time rescue medication use were also recorded.

Brusasco et al. (7) performed a double-blind, randomized, parallel-group study over a period of 12 weeks in 397 adults with moderate asthma. Patients were given either 6 µg of Oxis Turbuhaler b.i.d., terbutaline (0.5 mg q.i.d. via Turbuhaler), or placebo. The primary efficacy variable was morning PEF, and Oxis Turbuhaler was significantly more effective than placebo or terbutaline throughout the study. Moreover, Oxis Turbuhaler was significantly more effective in reducing daytime and

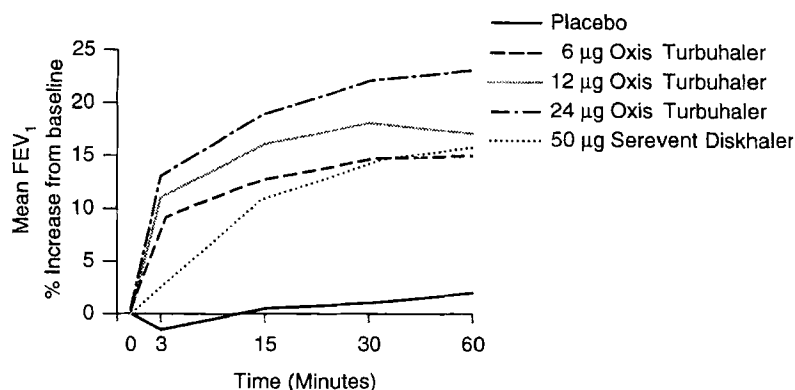


Fig. 3. Onset of action of Oxis Turbuhaler compared with salmeterol at 50 µg via Diskhaler and placebo (5).

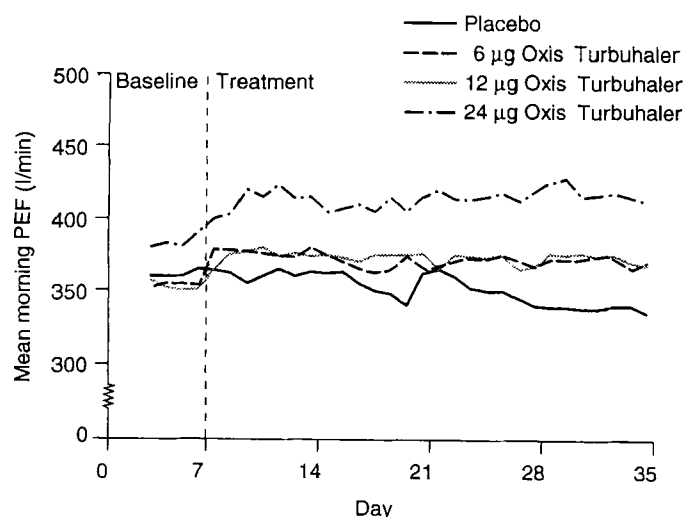


Fig. 4. Increase in morning PEF after treatment with Oxis Turbuhaler or placebo (6).

night-time symptom scores with a concomitant decrease in the use of rescue medication.

The additional bronchodilating effect of terbutaline, after treatment with Oxis Turbuhaler, was also determined in this study. Patients were given one dose of 6 µg Oxis Turbuhaler and, 15 min later, a further dose of terbutaline (1.25 mg). The primary outcome variable, FEV₁, was determined at the beginning of the study (after run-in) and compared with measurements obtained after 3 months of treatment with Oxis Turbuhaler. In all cases, the maximum bronchodilatation achieved did not change over the study period (Fig. 5). This indicates that treatment with Oxis Turbuhaler does not induce tachyphylaxis. Similar results were seen in the other treatment groups, and this has been repeated in other clinical studies (8).

Maintained clinical efficacy

A double-blind, placebo-controlled study with formoterol was performed over 6 months in 239

patients with moderate asthma (68–66% predicted FEV₁; all were using inhaled corticosteroids) (9). The objective of the study was to investigate the long-term efficacy of a higher dose of Oxis Turbuhaler, 24 µg (b.i.d.). Primary variables were changes in total asthma symptom score and morning PEF between the run-in period and the end of the treatment period. An immediate improvement in morning PEF was recorded in patients receiving Oxis Turbuhaler at 24 µg after the run-in period. This was maintained at a similar level over the study period (mean increase 26 l/min from run-in to the last 4 weeks of treatment) and was followed by a drop in airway function when treatment was discontinued. Airway function was reduced by 2 l/min in the placebo group, and the difference between the formoterol group and the placebo group was significant (Fig. 6). The asthma symptom score showed a decrease of 1.3 from 3.6 vs the placebo group, and Oxis Turbuhaler was also more efficacious in improving evening PEF and reducing the need for rescue medication.

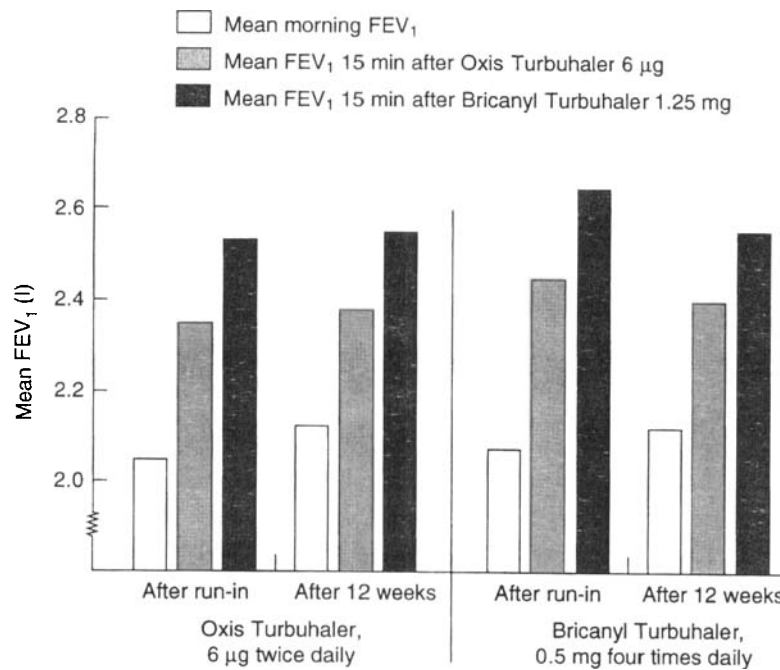


Fig. 5. Immediate bronchodilating effect of study drugs and additional β_2 -adrenergic agonist after run-in and 12 weeks' treatment (7).

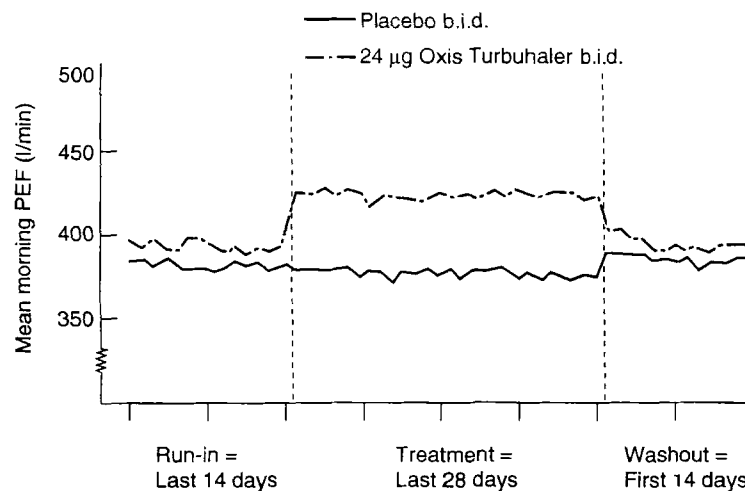


Fig. 6. Increase in morning PEF after treatment with Oxis Turbuhaler (24 µg) or placebo b.i.d. (9).

The drop in mean PEF observed after cessation of treatment is characteristic and generally observed with long-acting bronchodilators. However, the mean PEF during the washout period did not fall below the placebo levels and was higher than the run-in values for the same group. This indicates that Oxis Turbuhaler is not associated with rebound bronchoconstriction. Methacholine provocation experiments were performed at four treatment centres. Data before and after 6 months' treatment were available from 40 patients in the placebo group and 49 patients in the Oxis Turbuhaler group. There was no statistically significant difference in reactivity between the two groups. Therefore, Oxis

Turbuhaler treatment was not associated with an increase in hyperresponsiveness. In summary, it appears that the response to Oxis Turbuhaler is well maintained (up to a period of 6 months), that the response to additional bronchodilators is also maintained (up to 3 months), and that there is no clinical evidence for rebound bronchoconstriction or hyperresponsiveness with regular Oxis Turbuhaler use.

Safety and adverse events

In the four multiple-dose studies mentioned in this review, a total of 1199 patients were exposed to

either Oxis Turbuhaler (6, 12, and 24 µg b.i.d.), terbutaline, or placebo (6–9). Some 65% of the patients from all treatment groups reported at least one adverse event during the studies. Adverse events relating to the respiratory system were the most frequently reported (37% of patients) and probably reflect the underlying disease. Adverse events typical of treatment with β_2 -adrenergic agonists were not prominent. However, tremor was reported by 2% of patients in the 6 µg b.i.d. Oxis Turbuhaler group, 4% in the 12 µg b.i.d. Oxis Turbuhaler group, and 12% in the 24 µg b.i.d. Oxis Turbuhaler group. In comparison, tremor was reported by 5% of the terbutaline-treated patients and by none of the placebo-treated patients. Headache (21–25%), muscular cramp (1–2%), and palpitations (1–2%) were equally distributed among Oxis Turbuhaler, placebo, and terbutaline treatment groups.

The incidence of serious adverse events during treatment in these studies was Oxis Turbuhaler 1%, placebo 2%, and terbutaline 3%. Furthermore, only 2% of patients treated with Oxis Turbuhaler, 2% with placebo, and 3% with terbutaline discontinued treatment early because of adverse events. These results indicate that Oxis Turbuhaler is well tolerated and safe for clinical use.

The safety effects of Oxis Turbuhaler at high doses have also been assessed in a number of studies. A four-way, crossover, double-blind study was performed in 11 patients who received 6 µg of formoterol 3+3+6 times (18+18+36 µg) to a total dose of 72 µg over 12 h (10). Salbutamol was also given as reference therapy at 300+300+600 µg or at a dose three times higher, to a total of 1200 µg or 3600 µg, respectively. Prior to the study, all patients were receiving regular treatment with Oxis Turbuhaler. All doses of formoterol produced an initial decrease in serum potassium, an effect which is similar to the effects of all known β_2 -adrenergic agonists. However, a recovery in serum potassium was observed with continued Oxis Turbuhaler administration over 12 h, and this paralleled the improvement seen with salbutamol. Therefore, it appears that the systemic effects of formoterol are short-lasting and similar to those observed with short-acting β_2 -adrenergic agonists. This suggests that Oxis Turbuhaler can be taken in high doses without the occurrence of serious side-effects.

A further two-part study administered multiple doses of 6 µg Oxis Turbuhaler or 0.5 mg of terbutaline Turbuhaler to 12 and 15 patients, respectively, over three consecutive days (11). In the first part ($n=12$), the effects of cumulative daily doses of 72 µg Oxis Turbuhaler were compared with the effects of 6 mg of terbutaline Turbuhaler on serum potassium, pulse, heart rate, blood pressure, and a

number of electrocardiogram variables including QTc. In the second part, doses of 120 µg Oxis Turbuhaler were compared with 10 mg terbutaline Turbuhaler ($n=15$). In the first part, terbutaline 6 mg showed greater systemic effects than Oxis Turbuhaler 72 µg on pulse, blood pressure, heart rate, and QTc. In the second part, terbutaline 10 mg had significantly greater effects on serum potassium levels, pulse, heart rate, and QTc than Oxis Turbuhaler 120 µg. Furthermore, tolerance to the hypokalaemic effect was seen to develop despite the fact that these patients were regularly using short-acting β_2 -adrenergic agonists.

This study demonstrates that Oxis Turbuhaler is less systemically active than terbutaline when taken in high doses. However, the doses administered are not equipotent but represent the cumulative doses that would be achieved if the same number of doses were taken as rescue medication. This study aimed to demonstrate that if a patient utilized Oxis Turbuhaler as rescue medication, instead of taking it once or twice daily for long-term symptom relief, there would be no safety implications.

Summary

Oxis Turbuhaler has been approved for use in Europe at doses of 6, 12, or 24 µg once or twice daily. It has a rapid onset of action (within minutes) and demonstrates a maintained effect on airway function (an improvement of 20–30 l/min in PEF is seen 12 h after dosing), and it is well tolerated and safe. It decreases the incidence of acute asthma attacks, stimulates an immediate increase in PEF (in the order of 40–45 l/min), is effective when given in conjunction with anti-inflammatory medication, and has been shown to maintain a level of asthma control in all studies performed. Hence, Oxis Turbuhaler is a clinically relevant tool for use in patients receiving inhaled corticosteroids who require additional control of their asthma symptoms.

Discussion

Audience: Professor Pauwels showed that the duration of action of Oxis Turbuhaler at 6 and 12 µg was approximately 6–7 h ($FEV_1 >15\%$ over baseline). It is known that the efficiency of Turbuhaler is dependent upon an adequate inspiratory airflow (60 l/min). Have you studied the duration of action of these marketed doses in patients with low inspiratory airflows?

O. Selroos: Compared with placebo, the duration of action was 12 h. Concerning the inspiratory flow through Turbuhaler, it should be noted that no

difference in efficacy has been seen at inspiratory flows through Turbuhaler of 40 and 60 l/min. There are very few asthmatic patients who cannot produce a flow of 40 l/min through Turbuhaler, and these patients can usually be taught to inhale more forcefully, thereby achieving the required inspiratory flow.

Audience: If formoterol has a duration of action of 6–7 h, are patients having to use the Oxis Turbuhaler more than twice a day to maintain bronchodilatation over 12 h?

O. Selroos: This has not occurred in any of the patients in these studies, as, compared with placebo, the duration of action is 12 h. Because of the diurnal variation in airway calibre, the duration of action should always be based on the comparison with placebo, not with baseline.

Audience: Do you have experience with formoterol in exercise-induced asthma and are there any side-effects?

O. Selroos: Yes, we are performing studies in children and adults with Oxis Turbuhaler in exercise-induced asthma. Compared with short-acting β_2 -adrenergic agonists, formoterol provides protection for a much longer time, 7–12 h. If patients have been exposed to β_2 -adrenergic agonists before, then usually there are no side-effects. If, however, patients take formoterol only on demand, tremor and tachycardia may occur.

Audience: Is the particle size the same in all three drugs that you have produced for Turbuhaler?

O. Selroos: The percentage of small particles, below 5 μm , is slightly higher in the formoterol preparation, which gives a higher deposition. Turbuhaler usually delivers 25–30% of the metered dose to the airways, compared with around 10–15% with ordinary pressurized metered-dose inhalers. With this

preparation, almost 40% of the metered dose is deposited in the lung.

References

1. Faulds D, Hollingshead LM, Goa KL. Formoterol. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991;42:115-37.
2. Löfdahl C-G, Svedmyr N. Formoterol fumarate, a new β_2 -adrenoceptor agonist. Acute studies of selectivity and duration of effect after inhaled and oral administration. *Allergy* 1989;44:264-71.
3. Wetterlin K. Turbuhaler® – a new powder inhaler for administration of drugs to the airways. *Pharmacol Res* 1988;5:506-8.
4. Ringdal N, Derom E, Pauwels R. Onset and duration of action of single doses of formoterol inhaled via Turbuhaler® in mild to moderate asthma. *Eur Respir J* 1995;8:68s.
5. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lötvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997;10:2484-9.
6. Schreurs AJ, Sinninghe Damste HE, de Graaff CS, Greefhorst AP. A dose-response study with formoterol Turbuhaler® as maintenance therapy in asthmatic patients. *Eur Respir J* 1996;9:1678-83.
7. Brusasco V, Ringdal N, Ekström T, Sobradillo V. Effect of formoterol 6 mcg b.i.d. via Turbuhaler® for 3 months in asthma: comparison with terbutaline and placebo. *Eur Respir J* 1995;8 Suppl 19:158s.
8. Ekström T, Ringdal N, Tukiainen P. Formoterol Turbuhaler® 12 μg b.i.d. improves lung function in asthmatic patients compared with terbutaline and placebo. *Eur Respir J* 1995; 8 Suppl 19:157s.
9. van der Molen T, Postma DS, Turner MO, et al. Effects of the long-acting β -agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1997;52:535-9.
10. Lötvall J, Persson G, Larsson P, Mardell C, Rosenborg J. Tolerability of inhaled high doses of formoterol and salbutamol in asthmatic patients maintained on twice daily formoterol 12 μg (9 μg delivered). *Eur Respir J* 1997;10 Suppl 25:103s.
11. Falck M, Huhti L, Sutinen E, et al. Formoterol Turbuhaler® 72 and 120 μg (delivered doses 54 and 90 μg , respectively) daily during three days was safe in patients with asthma. *Eur Respir J* 1997;10 Suppl 25:103s.