Rhinology, 35, 58–62, 1997

Common cold and high-dose ipratropium bromide: Use of anticholinergic medication as an indicator of reflex-mediated hypersecretion*

Birgitte Østberg, Birgit Winther†, Peter Borum, Niels Mygind

Otopathological Laboratory, Department of Otorhinolaryngology, Rigshospitalet, Copenhagen, Denmark

SUMMARY

It was our aim to study the role played by parasympathetic reflexes for the amount and physical characteristics of nasal discharge during a common cold, and to define the maximum anti-rhinorrhoea effect obtainable with anticholinergic medication. Fifty adults with naturally acquired colds were treated with a very high dose of the topically active cholinoceptor-antagonist ipratropium bromide in a randomized, double-blind, placebo-controlled study of parallel groups. A dosage of 400 μg was given 4 times daily for 3 days, using a specially manufactured high-dose pressurized aerosol. This treatment resulted in a 56% reduction in the number of nose blowings ($p<0.01$) and a 58% reduction in the weight of blown secretions ($p<0.01$). Assessment of the "pourability" of the nasal discharge indicated that ipratropium bromide mainly reduces the watery secretions but not the mucopurulent secretions. The high dose of ipratropium bromide caused nose- and mouth dryness in a considerable number of the patients. In conclusion: (1) during the first days of a common cold about 60% of the nasal discharge is a reflex-mediated product from nasal glands; (2) this type of secretion is predominantly watery; and (3) ipratropium bromide can reduce watery rhinorrhoea in the common cold, but a lower dose is required in order to avoid side effects.

Keywords: nose, common cold, ipratropium bromide, nasal secretions

INTRODUCTION

The common cold is the most frequent airway disease (Gwaltney and Hayden, 1982). Prevention by vaccination is not possible due to the high number of common cold viruses, and there is no antiviral compound for clinical usage (Gwaltney and Hayden, 1982). Consequently, only symptomatic remedies are available and their efficacy is not convincing. Acetylsalicylic acid is widely used, but its effect on nasal symptoms has not been documented (Sperber et al., 1992). Antihistamines are also used, but controlled studies have, on the whole, failed to show superiority over placebo (West et al., 1975; Smith and Geldman, 1993). Adrenoceptor agonists, as vasoconstrictors, are of documented efficacy, but only for nasal blockage (Winther et al., 1983).

We have earlier reported that the cholinoceptor-antagonist ipratropium bromide (IB; 320 μg/day), as a pressurized nasal aerosol, can reduce nasal discharge during a common cold (Borum et al., 1981), and recently two large studies have extended these results to an aqueous solution of IB (Dockhorn et al., 1992; Diamond et al., 1995). In the present study we have used a very high dose of IB (1,600 μg/day) as an investigative tool in order to identify the part of nasal discharge that is a parasympathetic, reflex-mediated glandular product and with that define the maximum anti-rhinorrhoea effect of anticholinergic therapy.

PATIENTS AND METHODS

Patients

Medical students and members of the hospital staff were recruited for the trial by advertisement. They were requested to come as early as possible after catching a cold. The subjects were included in the study provided they fulfilled the following criteria: (1) felt confident that they had caught a cold; (2) had suffered from sneezing attacks and rhinorrhea for less than 24 h (throat symptoms for less than 36 h); (3) had no history of allergic disease, chronic recurrent airway disease, or frequent complications to colds (otitis media, sinusitis, bronchitis); (4) did not use any medication; (5) were able to produce at least 0.2 ml of nasal secretion during a 15-min observation period; (6) showed obvious signs of rhinitis during the observation period

* Received for publication August 16, 1996; accepted November 15, 1996

† Present adress: Department of Otolaryngology/Head and Neck Surgery, University of Virginia, Charlottesville, Virginia, USA

(red nose, sneezing, discharge, blockage, rhinolalia); and (7) gave informed consent to participate. Fifty subjects, who fulfilled these criteria, were enrolled in the study; 33 were women and 17 men. Their mean age was 30.7 years (range: 20-55 years). The protocol was approved by the Ethical Committee of Copenhagen.

Medication

The patients were allocated at random to treatment with IB or placebo; there were 26 patients in the IB group and 24 patients in the placebo group. IB, as a micronized powder, was propelled by CFC gas (Freon) from a pressurized canister, equipped with a nasal adaptor. The dose was 2 puffs – each of 100 μg IB – in each nostril 4 times daily (total dose of 1,600 μg/day) for 3 days. All subjects continued their normal routine during the treatment period. They were not allowed to take any other medication.

Coded aerosols were provided by Boehringer Ingelheim (Ingelheim, Germany). The high-dose aerosols, delivering 100 μg/puff, were specially manufactured for the trial. The commercially available IB aerosols, used for the nose and bronchi, deliver 20 μg/actuation.

Design of the trial

The trial was performed as a double-blind, placebo-controlled, randomized study of two parallel groups.

Recording of symptoms

The patients started symptom recording immediately after the first medication, and the following 24 h are referred to as "day 1."

Number of sneezes and nose blowings: The patients carried a diary card on which they recorded every sneeze and every nose blowing. They gave a self-assessment score every hour for nasal blockage, and a mean symptom index for blockage was calculated for each day. This method has been described in detail earlier (Toft et al., 1982).

Weight of nasal discharge: The patients were instructed not to sniff and only to blow their nose in a pre-weighed plastic vial (of the type used for sputum sampling), one for each of the 3 days. The vials were kept in the refrigerator and brought to the hospital at the end of the trial. The total amount of secretions produced on each of the 3 days was measured by weighing.

Physical characteristics of secretions: All samples of secretion were examined and the plastic vial was tilted until its content dropped down in a waste container. Each sample was given a score of "pourability" from 1 to 10 ranging from the samples adhering to the vial (score 1) and to those that moved instantaneously like water when the vial was tilted and reversed (score 10). This simple examination, described by Keal and Reid (1970), was carried out by two of the investigators before the code was broken.

Side effects: After the last medication the patients completed a questionnaire about a series of symptoms, some of which were well-known anticholinergic effects and some were irrelevant to the trial drug. They were graded as "0" (absent), "1" (of no significance for clinical use of the drug); "2" (between 1 and 3), and "3" (prohibitive for clinical use of the drug).

Statistics

A non-parametric test for unpaired data (Wilcoxon's rank sum test) was used with two-sided alternatives.

RESULTS

All patients who entered the study completed the treatment and were included in the assessment of effects and side effects.

There was no difference between the IB- and placebo groups with regard to the daily number of sneezes, and the nasal blockage index (Table 1).

Table 1. Number of sneezes and nasal blockage index in the two treatment groups (NS: not significant).

	ipratropium bromide (n=26)	placebo (n=24)	p-value
number of sneezes			
day 1	8.0±1.2	8.6±1.6	NS
day 2	4.8±0.9	6.7±1.1	NS
day 3	4.2±0.9	4.1±0.9	NS
blockage index			
day 1	2.89±0.20	2.90±0.20	NS
day 2	2.63±0.20	2.98±0.25	NS
day 3	2.51±0.23	2.69±0.26	NS

The IB-treated patients had significantly fewer nose blowings ($p<0.01$; Figure 1) and significantly lower weights of nasal discharge ($p<0.01$; Figure 2) on all study days, as compared to the placebo-treated group. The overall reduction was 56% for the number of nose blowings and 58% for the weight of secretions. There was approximately the same percentage effect on all 3 days.

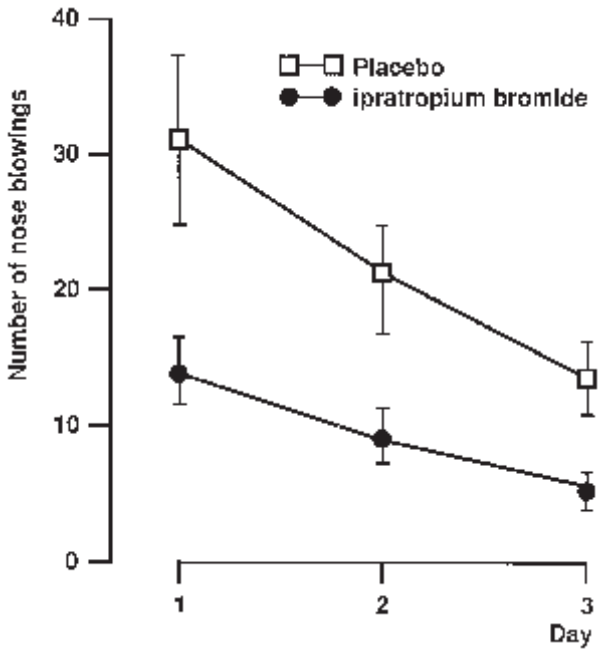

Figure 1. Number of nose blowings (mean±SEM) in common cold patients treated with high-dose ipratropium bromide (N=26) or with placebo (N=24) ($p<0.01$ for all days).

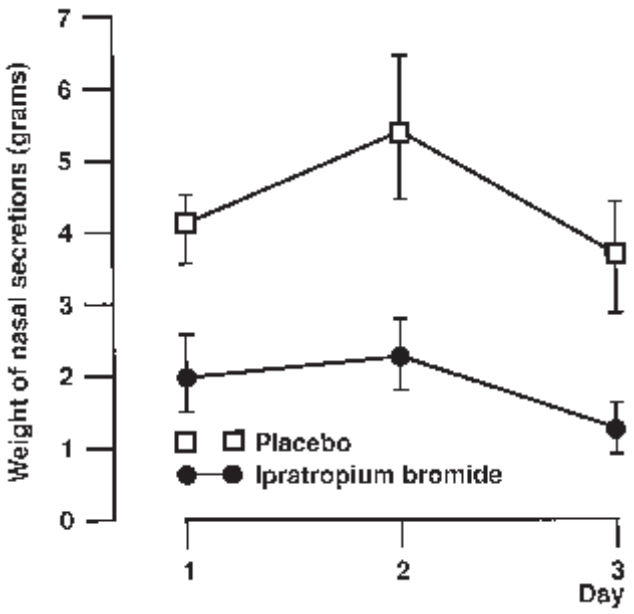

Figure 2. Weight of nasal secretions (mean±SEM) in common cold patients treated with high-dose ipratropium bromide or with placebo ($p<0.01$ for all days).

The mean score for "pourability" of the secretions was significantly lower in the IB group than in the placebo group ($p<0.01$; Figure 3). A comparison between the total weight of IB-secretions and of placebo-secretions within the single-score groups (Figure 4) indicates that the physical characteristics of the nasal secretions change quantitatively as well as qualitatively when patients are treated with a high dose of IB. Such patients produced secretions with physical characteristics (score 1 to 2) not seen in untreated patients.

Although watery rhinorrhoea is a characteristic symptom of the common cold, most patients (24 in the IB group and 17 in the

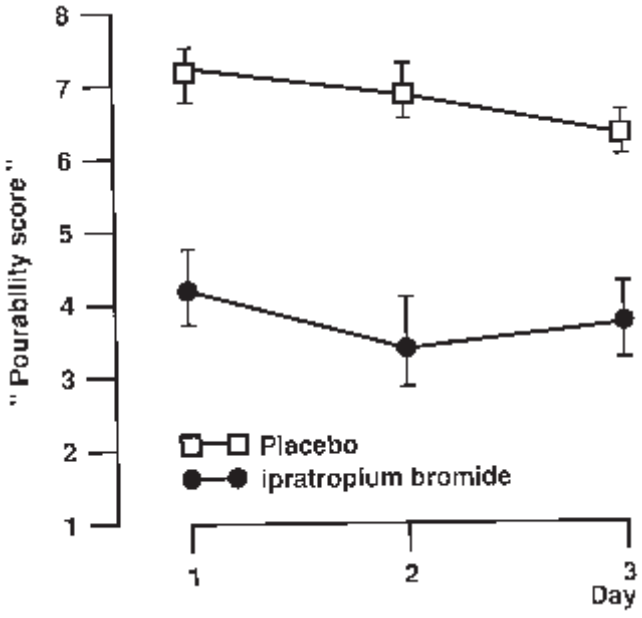

Figure 3. Score for "pourability" of nasal secretions (mean±SEM) in common cold patients treated with high-dose ipratropium bromide and with placebo ($p<0.01$ for all days).

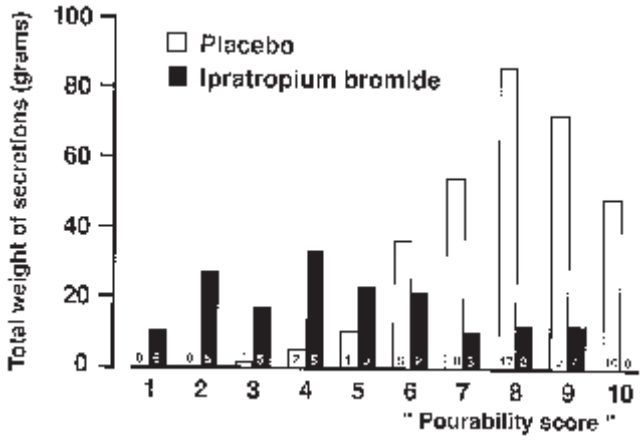

Figure 4. Score for "pourability" of nasal secretions in common cold patients treated with high-dose ipratropium bromide or with placebo. The columns represent the total weight of all secretions having a certain score. The figures in the columns refer to the number of samples given that score. Not all patients were able to produce a measurable sample on all 3 days, and the number of samples available for examination was smaller in the ipratropium group (40 of an expected 78) than in the placebo group (58 of an expected 72).

placebo group) also complained of having nasal dryness (Table 2), probably related to the marked diurnal variation of secretory activity in the nose with low secretory rates, and risk of nasal dryness in the evening and at night (Smolensky et al., 1995). The sensation of nasal dryness was considered prohibitive for clinical use of the drug by 12 patients in the IB group and by 1 patient in the placebo group ($p<0.01$). Unacceptable mouth dryness occurred in 10 patients in the IB group and in 2 patients in the placebo group ($p=0.05$). Other symptoms of systemic anticholinergic activity were not reported (Table 2).

DISCUSSION

Clinical effect

The few placebo-controlled studies of the anti-rhinorrhoea effect of IB in the common cold have shown an effect, but to a varying degree. Borum et al. (1981) treated patients with a pressurized aerosol (80 μg, four times a day), and there was a 34% overall reduction of symptom scores. The treatment was clinically beneficial only during the first days of the cold when rhinorrhoea was profuse and watery.

In two large US studies, IB was given as an aqueous solution from a pump spray. Using a dose of 168 μg four times daily, Dockhorn et al. (1992) found an 18-22% reduction in secretion weight and symptom score. Diamond et al. (1995), using three concentrations, found a dose-related increase in efficacy with a mean score improvement of 18% for the low dose (84 μg t.i.d.), 24% for the medium dose (168 μg t.i.d.), and 35% for the high dose (316 μg t.i.d.).

In the present study, a very high dose of IB pressurized aerosol (400 μg q.i.d.) reduced symptom scores and secretion weight with 56% and 58%, respectively. Thus, anticholinergic treatment can significantly reduce rhinorrhoea in the common cold, the non-viscous watery part of the secretion in particular (*vide infra*), and the treatment has the potential of abolishing watery nose dripping.

Table 2. Possible side effects noted in diary cards. Figures indicate number of patients.

	ipratropium bromide (N=26)				placebo (N=24)			
	no	slight	moderate	marked	no	slight	moderate	marked
malaise	23	2	3	0	14	7	3	0
diarrhea	26	0	0	0	24	0	0	0
palpitation	25	1	0	0	22	2	0	0
headache	20	2	4	0	12	7	4	1
nausea	23	2	0	1	21	2	1	0
abdominal pain	23	2	1	0	22	2	0	0
mouth dryness	6	2	8	10	11	7	3	2
dizziness	25	1	0	0	22	2	0	0
blurred vision	26	0	0	0	24	0	0	0
obstipation	25	0	1	0	21	1	2	0
nose dryness	2	5	7	12	7	7	9	1
dysuria	26	0	0	0	24	0	0	0
sensation of heat	23	3	0	0	20	2	2	0

Side effects

The maximum anti-rhinorrhoea effect of IB was associated with significant local side effects, and the very high dosage caused unpleasant side effects. It is interesting that the subjective sensation of dryness in the nose is not associated with a reduced mucociliary transport rate, as shown in another study of patients with perennial non-allergic rhinitis treated with the same dosage for two weeks (Kirkegaard et al., 1987). When IB pressurized aerosol is used in lower doses in clinical practice, the treatment causes less nasal dryness (Borum et al., 1979; Dolovich et al., 1987; Borum et al., 1983), especially when the dosage, in the single patient, is adjusted to the severity of the symptoms and to their diurnal variation (Smolensky et al., 1995).

Apparently, only the highest concentration of IB aqueous solution caused nasal dryness in about 10% of the patients in the study of Diamond et al. (1995). Other studies, also, have indicated that the aqueous solution may cause less dryness than the pressurized aerosol (Bronsky et al., 1995). On the other hand, the pressurized aerosol seems to be more potent and long-lasting than the aqueous solution, as indicated by a recent experimental study using methacholine-induced rhinorrhoea as the effect parameter (Borum et al., 1996).

Clinical use of ipratropium in common cold

As watery rhinorrhoea is an important symptom of the common cold, we shall try to give some practical recommendations for the use of ipratropium. In our first study (Borum et al., 1981), a pressurized aerosol was given at a fixed dose (80 μg) four times daily, but this may not be the best way of administering the drug for the following reasons. The severity of rhinorrhoea differs considerable from patient to patient and from time to time, and there is a marked diurnal variation with most symptoms in the morning (Smolensky et al., 1995). It seems therefore preferable to give a relatively high early-morning dose, matching the severity of the symptoms (80 μg, repeated until effect), and thereafter only to use the spray on an as-needed basis. As the duration of the drug may outlast the length of the symptomatic episode, an unpleasant sensation of nasal dryness can occur but it can be relieved by the instillation of saline.

It is important to realize that ipratropium treatment is monosymptomatic. It has no effect on sneezing or nasal blockage, nor will it be useful in patients with viscous mucus or purulent discharge from the nose and paranasal sinuses.

Role of parasympathetic nerves and nasal glands

The main purpose of the present study was to determine the role played by the parasympathetic nervous system and by reflex stimulation of the nasal glands in the formation of nasal discharge.

Our result of a 56-58% reduction of the nasal fluids in the IB-treated group shows that more than half of the nasal discharge, during the first days of a common cold, is a reflex-mediated product from nasal glands. This is somewhat less that the 73% reduction of cold-air-induced rhinorrhoea found in a similar high-dose IB study (Østberg et al., 1987) This difference can be expected between a purulent infectious disease and a non-purulent condition.

As our examination of the nasal discharge showed that the watery secretions almost disappeared, while the amount of mucopurulent secretions was not reduced by the treatment, we can conclude that the IB-sensitive watery rhinorrhoea is a product of parasympathetic stimulation of nasal glands, while this is not the case with the IB-resistent mucopurulent secretions. The obvious visco-elastic properties of purulent secretions, however, indicate that they also are a product of mucus-producing cells. Not all mucus produced in the nose can be expected to be IB-sensitive, as goblet cells are not under the control of the parasympathetic nervous system, and airway glands can be stimulated directly by a series of secretagogues (Lundgren and Shelhamer, 1990). The release of such secretagogues from inflammatory cells during a viral infection is a likely explanation of the IB-resistent secretions, which together with plasma exudation and mucus from paranasal sinuses account for approximately 40% of the total nasal discharge.

Physical properties

Our patients sampled all their nasal discharge during the study period, and it was possible to obtain measurable samples on 98 out of 150 days. These samples were examined by pouring the content from the vial into a waste container and observing to what degree they behaved as a liquid or as a gel. This measurement of "pourability" is very simple, requiring no advanced equipment. Keal and Reed (1970) found a significant and reverse correlation between the "pourability" and the viscosity, as measured by conventional viscosimetry, indicating that "pourability" can be used as a rough measure of viscosity.

Using this method we found marked differences not only between samples but also between the two treatment groups. The data shown in Figure 4 indicate that the high dose of IB not only reduces the amount of the most watery nasal discharge (score 7-10) by 86%, but it also increases the amount of the most "viscous" secretions (score 1-4) by a factor 15. Secretions with these physical characteristics scarcely occurred in the placebo group.

To our knowledge, this is the first study showing that anti-cholinergic medication can change the physical properties, probably the viscosity, of nasal airway secretions.

In conclusion, our study has shown that about 60% of the nasal discharge is a reflex-mediated product from nasal glands during the first days of a common cold. The production of this watery secretion can be almost abolished by aggressive anticholinergic medication, but such treatment is associated with nasal dryness and a change in the physical characteristics of the nasal discharge. When used in a lower dose, intranasal IB is an effective and well-accepted treatment of watery rhinorrhoea in the common cold.

REFERENCES

1. Borum P, Mygind N, Larsen FS (1979) Intranasal ipratropium: a new treatment for perennial rhinitis. Clin Otolaryngol 4: 407-411.
2. Borum P, Mygind N, Larsen FS (1983) Ipratropium treatment for rhinorrhea in patients with perennial rhinitis. An open follow-up study of efficacy and safety. Clin Otolaryngol 8: 267-272.
3. Borum S, Becker B, Mygind N, Borum P (1996) Comparison between the effect of ipratropium bromide as a pressurized aerosol and as an aqueous pump spray on methacholine-induced rhinorrhoea. Rhinology 34: 198-200.
4. Borum P, Olsen L, Winther B, Mygind N (1981) Ipratropium nasal spray: A new treatment for rhinorrhoea in the common cold. Am Rev Respir Dis 123: 418-420.
5. Bronsky EA, Druce H, Findley SR, Hampel FC, Kaiser H, Ratner P, Valentine MD, Wood CC (1995) A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. J Allergy Clin Immunol 95: 1117-1122.
6. Dockhorn RJ, Grossman J, Posner M, Zinny M, Tinkleman D (1992) A double-blind, placebo-controlled study of the safety and efficacy of ipratropium bromide nasal spray versus placebo in patients with the common cold. J Allergy clin Immunol 90: 1076-1082.
7. Diamond L, Dockhorn RJ, Grossman J, Kisicki JC, Posner M, Zinny MA, Koker P, Korts D, Wecker MT (1995) A dose-response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold. J Allergy Clin Immunol 95: 1139-1146.
8. Dolovich J, Kennedy L, Kazim F, Vickerson F (1987) Control of the hypersecretion of vasomotor rhinitis by topical ipratropium bromide. J Allergy Clin Immunol 80: 274-278.
9. Gwaltney Jr JM, Hayden F (1982) The nose and infection. In: DF Proctor, I Andersen (Eds.) The Nose: Upper Airway Physiology and the Environment. Elsevier Medical Press, Amsterdam, pp. 399-422.
10. Keal E, Reid L (1970) Méthodes d'étude des modifications de la sécretion bronchique et de sa viscosité. Poulmom Coeur 26: 52-58.
11. Kirkegaard J, Mølgaard F, Mygind N, Grahne B, Holopainen E, Malmberg H, Brøndbø K, Rønje T (1987) Ordinary and high-dose ipratropium in perennial nonallergic rhinitis. J Allergy Clin Immunol 79: 585-590.
12. Lundgren J, Shelhamer JH (1990) Pathogenesis of airway mucus hypersecretion. J Allergy Clin Immunol 85: 399-417.
13. Østberg B, Winther B, Mygind N (1987) Cold air-induced rhinorrhea and high-dose ipratropium. Arch Otolaryngol (Stockh) 113: 160-162.
14. Smith MG, Geldman W (1993) Over-the-counter cold medications: A critical review of the clinical trials between 1950 and 1991. JAMA 269: 2258-2263.
15. Smolensky MH, Reinberg A, Labrecque G (1995) Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: Treatment implications. J Allergy Clin Immunol 95: 1117-1122.
16. Sperber SJ, Hendley JO, Hayden FG, et al. (1992) Effects of naproxen on experimental rhinovirus colds: A randomized, double-blind, controlled trial. Ann Intern Med 117: 37-41.
17. Toft A, Wihl J-A, Toxman J, Mygind N (1982) Double-blind comparison between beclomethasone dipropionate as aerosol and as powder in patients with nasal polyposis. Clin Allergy 12: 391-401.
18. West S, Brandon B, Stolley P, Rumrill R (1975) A review of antihistamines and common cold. Pediatrics 56: 100-107.
19. Winther B, Brofeldt S, Borum P, Pedersen M, Mygind N (1983) Lack of effect on nasal discharge from a vasoconstrictor spray in common cold Eur J Respir Dis 64 (Suppl 128): 447-448.

Niels Mygind, MD
Department of Respiratory Diseases
University Hospital of Aarhus
DK-8000 Aarhus
Denmark