

Studies on Histamine Metabolism in Intrinsic Bronchial Asthma

LÖWHAGEN, O., GRANERUS, G. and WETTERQVIST, H.

Department of Allergology, First Medical Service and Department of Clinical Physiology, Sahlgrenska Hospital, University of Gothenburg, Sweden

Histamine metabolism was investigated in patients with intrinsic asthma, during the acute phase and in remission, by determination of the urinary excretion of histamine metabolites. During acute attacks the excretion of methylhistamine (MeHi) and 1-methyl-4-imidazoleacetic acid (MeImAA) was significantly increased compared with healthy subjects. The excretion of MeHi was significantly increased during acute attacks compared with remission. The excretion of MeImAA was also increased, but the difference was not significant. The correlation between the excretion of MeHi and MeImAA was highly significant. Corticosteroids, given to some patients during remission, did not affect the excretion of histamine and its metabolites. Smoking and respiratory infection during the acute attacks were both accompanied by increased excretion of MeHi. The results indicate that there is an increased histamine turnover in acute attacks of intrinsic bronchial asthma.

Key words: asthma; corticosteroids; histamine metabolism; respiratory infection; smoking

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Histamine has been related to the asthmatic reaction, mainly on the basis of its pharmacological effects and *in vitro* studies of the allergen-induced histamine release from sensitized cells and tissues (1).

Earlier *in vivo* studies in asthmatic patients, including determination of the histamine (Hi) concentration in whole blood and urine, have not given any consistent findings indicating a role for histamine in asthma. (6, 7, 10, 14, 15, 18, 19).

A convincing elevation of the plasma concentration of histamine (Hi) has recently been demonstrated after provocation with allergen (4) and aspirin (22). Simon et al. (21) also found elevated plasma histamine concentrations during both extrinsic and intrinsic asthmatic attacks.

Histamine is very rapidly inactivated and in order to obtain an accurate measure of the total release, the urinary excretion of histamine metabolites has to be determined (25). Furthermore, a histamine-restricted diet is a necessary requirement when endogenous histamine turnover is to be evaluated. Only a few studies of this type have been performed.

Thom et al. (23) investigated children with mild to moderate asthmatic attacks and did not find any significant increase in the excretion of the main metabolite, 1-methyl-4-imidazole-acetic acid (MeImAA). In a similar study in asthmatic children with acute symptoms in which the urinary excretion of histamine, MeImAA and the intermediate metabolite, methylhistamine (MeHi), was measured, Mitchell et al. (16) were unable to

detect any significant change in histamine metabolism.

The aim of this study was to investigate the daily histamine turnover on adult patients suffering from severe attacks of intrinsic bronchial asthma by measuring the urinary excretion of histamine metabolites, and to study the possible influence of other factors.

PATIENTS AND METHODS

Thirty-nine patients, aged 16–71 years, with intrinsic bronchial asthma (1) were selected for the study. Some data on the patients are given in Table 1.

Experimental procedure

The investigation was divided into three parts. In Part 1 the urinary excretion of MeHi was investigated in 27 patients treated for acute attacks of intrinsic asthma, defined as a state when the standard medication became insufficient. In Part 2 both MeHi and MeImAA were determined in six patients during acute attacks of intrinsic asthma and later in remission. In Part 3 the urinary excretion of Hi, MeHi and MeImAA was determined in six other patients with intrinsic asthma in remission who were given corticosteroids for 2 or 6 days.

Part 1. All patients were admitted to the hospital for further treatment after varying duration of progressing symptoms, usually 1–2 weeks. The treatment included corticosteroids, theophyllines, β -adrenergic stimulants and expectorants. Initially, all patients were treated with parenteral corticosteroids between 1 and 10 days (mean 4.6 days). After that, oral steroids in decreasing doses were used (Fig. 1). Most patients were given betamethasone but a few received hydrocortisone or prednisolone. The potency per unit weight of hydrocortisone, prednisolone and betamethasone with regard to the antiasthmatic effect was assumed to be 1:5:50 (2).

Twelve patients were treated with tetracyclines because of concomitant respiratory infection. The diagnosis was established clinically on the basis of fever, presence of discoloured sputum or sensation of infection in the respiratory tract. Smoking, defined as a daily consumption of more than 10 cigarettes during the last year, was reported by seven patients.

Urine collection was started at 7 a.m. on the first or second day after admission to the hospital and continued for 3–7 days. To ensure uniformity, the first whole 24-h period was called "day 1". During the days of urine

Table 1.

Selected data of the patients in the three parts of the study. Number of patients with regular need for corticosteroids during the preceding year, numbers of smokers, and numbers with respiratory infections during the acute attack are given. Duration of the asthmatic disease and number of days of parenteral corticosteroid therapy during the acute attack are given as the means $\pm$ s.d. and ranges

	n	Females	Males	Age (years)	Duration of asthma (years)	Regular cortisone	Smokers	Respiratory infection	Parenteral cortisone (days)
Part 1	27	14	13	16–71	20 $\pm$ 19 (1 – 64)	16	7	12	4.6 $\pm$ 2.5 (1 – 10)
Part 2	6	2	4	19–71	8 $\pm$ 9 (1 – 19)	3	2	6	4.3 $\pm$ 0.8 (3 – 6)
Part 3	6	3	3	24–49	15 $\pm$ 13 (3 – 34)	0	3	0	0

collection the patients were given a special diet with a low content of bacteria and histamine (9). There were no other restrictions in the management and some patients were given other drugs, such as hypnotics, antihistamine and analgesics. Two patients were treated for other diseases apart from asthma (hypothyroidism and mental depression).

Part 2. The patients were admitted and treated for acute attacks of intrinsic asthma in the same way as in Part 1. Initially corticosteroids were given parenterally in all cases for 3–6 days, mean 4.3 days. After that, oral steroids in decreasing doses were given (Fig. 1). During the remission four patients still needed daily oral corticosteroids but in much lower doses (Fig. 1).

All patients presented signs of respiratory infection during the acute phase and were treated with tetracyclines. Two patients were smokers.

During the acute phase urine collection was also started at 7 a.m. on the first or second day after admission and continued for 3–6 days. During the remission, 5–11 months later, urine was collected for 2–4 days. The same diet as in Part 1 was prescribed during the periods of urine collection.

Part 3. Six other patients were investigated in remission. None needed regular corticosteroids, but all patients were using bronchodilators as required.

Four of the patients were given prednisolone, 25 mg orally, for 2 consecutive days. The same diet as before was prescribed and urine for determination of Hi, MeHi and MeImAA was collected on 2 days before, during, and on 2 days after the steroid medication.

Two of the patients were given prednisolone, 30 mg orally, for 6 consecutive days. Urine for determination of MeImAA was collected on 3 days before, during, and on 3 days after the steroid medication. No special diet was prescribed for these patients.

Laboratory procedures

All urine samples were collected in 24-h portions and stored in glass bottles containing 100 ml of 1 mol/l hydrochloric acid.

Histamine. Urinary histamine was determined by bio-assay on isolated guinea-pig ileum after the purification of histamine by adsorption onto a Dowex-50 cation exchange resin (26). The mean recovery was $86 \pm 8\%$. All values were expressed as the "free base" and were corrected for recovery.

Methylhistamine. MeHi was determined by reaction with 2-4-dinitrofluorobenzene, followed by separation of reaction products by thin-layer chromatography and spectrometric measurement of eluates from the chromatogram (9, 27). The mean recovery was $77 \pm 7\%$. The values were corrected for recovery and expressed as the "free base".

1-Methyl-4-imidazoleacetic acid. Urinary MeImAA was determined according to the method of Granerus & Magnusson (8) with slight modifications (9). After evaporation of the urine, esterification with ethanol, extraction with ether and separation on a cellulose column, the final separation and quantification was done by thin-layer chromatography. The values were corrected for recovery using an internal standard of ^{14}C -MeImAA (11).

Control values. The mean excretion of Hi, MeHi and MeImAA with the applied methods and diet in 20 healthy subjects, aged 19–58 years, (9) is shown in Table 2.

Statistical procedures

Standard methods were used for calculation of means, standard deviations (s.d.), standard errors of the mean (s.e.) and correlation coefficients (r). Differences between means were analysed by using Wilcoxon's rank sum test. Individual differences between values

Table 2

Urinary excretion of histamine (Hi), methylhistamine (MeHi) and 1-methyl-4-imidazoleacetic acid (MeImAA) in 20 healthy subjects. All values are expressed in $\mu\text{g}/24\text{ h}$ and are corrected for recovery. The values of Hi and MeHi are expressed as "free base"

	Hi	MeHi	MeImAA
<i>n</i>	20	20	20
Mean	26	190	2700
S.d.	12	60	700
S.e.	3	20	200

during the acute phase and in remission were tested by Wilcoxon's test for paired differences. Correlations between histamine metabolites and doses of corticosteroids and urine volumes were analysed by Pittman's test, where correlations within each patient (Pittman-statistics) were weighted together (17). Two-tailed tests were used and differences were considered significant for P -values <0.05 .

RESULTS

Histamine metabolism

Part 1. Acute asthma (Table 3). The mean urinary excretion of MeHi was significantly increased on all 7 days compared with the control values. The excretion was greatest during the first 5 days. A significant decrease was observed on days 6 and 7 compared with days 2-4.

Table 3

Urinary excretion of methylhistamine (MeHi) in 27 patients during acute attack of intrinsic bronchial asthma. Collection of urine was started the first (day 1) or second day after admission to hospital and continued for 3-7 days

Acute asthma. MeHi $\mu\text{g}/24\text{ h}$							
Day	1	2	3	4	5	6	7
<i>n</i>	10	23	25	25	18	19	8
Mean	330	420	400	420	340	280	270
S.d.	80	200	190	180	160	120	100
S.e.	20	40	40	40	40	30	30

Part 2. Acute asthma and remission (Table 4). The mean excretion of MeHi during all days of acute asthma was higher than the control values. The differences were significant during days 2-6. The peak excretion was found on day 4.

The mean excretion of MeHi during all days of acute asthma was higher than the mean excretion during remission. On testing the individual differences, a significantly higher excretion was found on days 2-4.

The mean excretion of MeHi during remission was not significantly different from the control values.

Table 4

Urinary excretion of methylhistamine (MeHi) and 1-methyl-4-imidazoleacetic acid (MeImAA) in six asthmatic patients during acute attack and during remission, 5-11 months later

Acute asthma. MeHi $\mu\text{g}/24\text{ h}$						
Day	1	2	3	4	5	6
<i>n</i>	2	6	6	6	4	3
Mean	250	360	480	570	480	420
S.d.	50	150	230	230	250	250
S.e.	40	60	90	90	130	150

Acute asthma. MeImAA $\mu\text{g}/24\text{ h}$						
Day	1	2	3	4	5	6
<i>n</i>	2	6	6	6	4	3
Mean	2400	3700	4000	4300	5200	4300
S.d.	100	1300	1400	500	1700	2300
S.e.	100	500	600	200	900	1300

Remission. MeHi $\mu\text{g}/24\text{ h}$				
Day	1	2	3	4
<i>n</i>	6	6	4	2
Mean	200	200	220	220
S.d.	150	90	120	90
S.e.	60	40	60	60

Remission. MeImAA $\mu\text{g}/24\text{ h}$

Day	1	2	3
<i>n</i>	6	6	2
Mean	3200	3200	2800
S.d.	900	1200	100
S.e.	400	500	100

Table 5

Urinary excretion of histamine (Hi), methylhistamine (MeHi) and 1-methyl-4-imidazoleacetic acid (MeImAA) in four patients with intrinsic bronchial asthma during a symptom-free interval. During days 3 and 4 a daily dose of 25 mg prednisolone was given orally

Asthma in remission							
Hi $\mu\text{g}/24 \text{ h}$	Day	1	2	3	4	5	6
<i>n</i>		4	4	4	4	4	4
Mean		47	29	42	29	41	30
S.d.		20	22	14	16	31	25
S.e.		10	11	7	8	16	13

MeHi $\mu\text{g}/24 \text{ h}$	Day	1	2	3	4	5	6
<i>n</i>		4	4	4	4	4	4
Mean		320	320	330	330	260	210
S.d.		210	290	170	270	130	120
S.e.		110	140	90	130	70	60

MeImAA $\mu\text{g}/24 \text{ h}$	Day	1	2	3	4	5	6
<i>n</i>		4	4	4	4	4	4
Mean		4600	3300	3500	3300	3300	2900
S.d.		1100	2000	1100	1700	1100	1000
S.e.		600	1000	500	900	600	500

The mean excretion of MeImAA during days 2–6 was increased compared with the control values. The increase was significant during days 3–5.

The mean excretion of MeImAA during all days of acute asthma was higher than the mean excretion during remission, except day 1. On testing the individual differences the increase was not significant.

Table 6

Mean urinary excretion of MeImAA ($\mu\text{g}/24 \text{ h}$) in two symptom-free asthmatic patients treated for 6 days (day 4–9) with prednisolone 30 mg/day. No special diet was prescribed

Day	1	2	3	4	5	6	7	8	9	10	11	12
Mean	4800	5500	5200	4500	4200	6600	4200	5800	6000	5000	4400	4900

The mean excretion during remission was not significantly different from the control values.

Part 3. Steroid treatment during remission (Tables 5, 6; Fig. 1). Oral treatment with 25 mg prednisolone (equivalent dose of betamethasone, 2.5 mg) for 2 consecutive days was not accompanied by any significant change in the mean excretion of Hi, MeHi and MeImAA compared with the preceding and following days. The mean values of Hi, MeHi and MeImAA were higher than the control values, but the differences were not significant, except for Hi and MeImAA during the first day.

Oral treatment with 30 mg prednisolone (equivalent dose of betamethasone, 3.0 mg) for 6 consecutive days was not accompanied by any significant changes in the mean excretion of MeImAA compared with the preceding and following days.

Parts 2 and 3. Correlations between Hi, MeHi and MeImAA. The correlation between the urinary excretion of MeHi and MeImAA (Parts 2 and 3) was highly significant ($r = 0.54$, $P < 0.001$). The mean ratio between MeHi and MeImAA was 1:11 during the acute phase (Part 2) and 1:19 during remission. The difference was significant.

The correlation between Hi and MeHi (Part 3) was significant ($r = 0.49$, $P < 0.02$), as was that between Hi and MeImAA (Part 3, $r = 0.47$, $P < 0.05$).

Factors that might be related to histamine metabolism
Sex. There were no significant differences between males and females in the excretion of

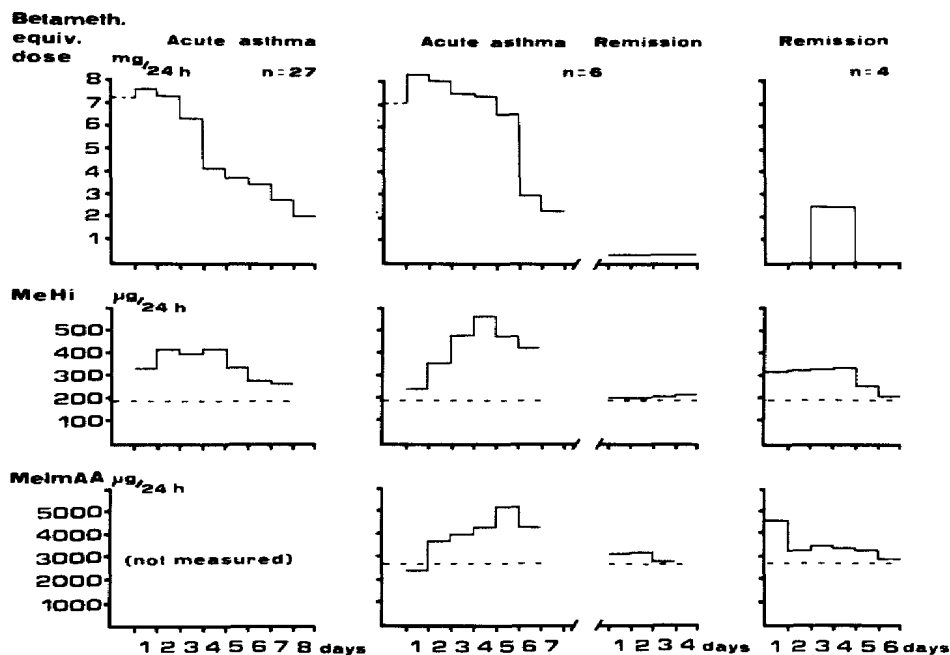


Fig. 1. Mean doses of corticosteroids (betamethasone equivalent dose) and mean excretion of MeHi and MeImAA during acute asthma and remission. Left diagrams illustrate Part 1 of the study, middle diagrams Part 2 and right diagrams Part 3. Mean excretion of controls is indicated by a hatched line.

MeHi and MeImAA during the acute phase (Parts 1 and 2).

Duration of asthmatic disease. There was no significant correlation between the duration of the asthmatic disease and the excretion of histamine metabolites (individual mean values) during the acute phase (Parts 1 and 2).

Need for regular corticosteroids. The excretion of histamine metabolites during the acute phase (individual mean values, Parts 1 and 2) was not significantly different in patients with and without need for regular cortisone therapy before admission.

Corticosteroids doses during acute asthma (Fig. 1). The correlation between MeHi and doses of corticosteroids during the acute phase (Parts 1

and 2) was not significant (Pitman's test, $P = 0.10$) but on the positive side. The correlation between MeImAA and doses of corticosteroids during the acute phase (Part 2) was also not significant (Pitman's test, $P = 0.88$).

Respiratory infection (Fig. 2). The mean values of MeHi during days 2–6 (Parts 1 and 2) were higher in patients with signs of respiratory infection than in non-infectious patients. The difference during day 3 was significant.

Smoking (Fig. 2). The mean values of MeHi on days 2–7 (Parts 1 and 2) were higher than in non-smokers but the differences were not significant.

Smoking and respiratory infection (Fig. 2). The mean values of MeHi in patients who were

Acute intrinsic asthma

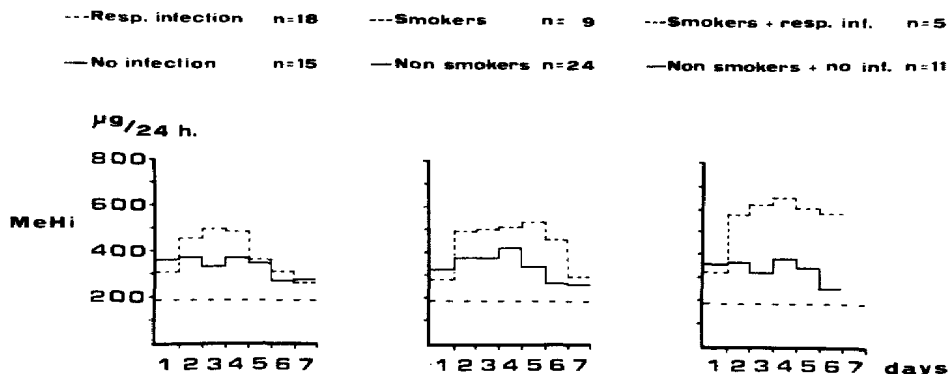


Fig. 2. Mean excretion of MeHi during acute phase of intrinsic bronchial asthma in 33 patients (Parts 1 and 2) divided on the basis of respiratory infection and smoking habits. Mean excretion of controls is indicated by a hatched line.

both smokers and infected, were higher than in those who were non-smokers and non-infected during days 2–6 (Parts 1 and 2). The difference was significant during days 3 and 4. The mean values of MeHi in both non-smoking and non-infected patients (Parts 1 and 2) were still significantly higher than the control values (where 7 out of 20 subjects were smokers) on days 1–5.

Urine volumes. The mean 24-h urine volumes (Parts 1 and 2) during days 1–7 were 1560, 1630, 1950, 2020, 1850, 1730 and 1620 ml respectively. No significant difference between these volumes was found. The correlation between MeHi and 24-h urine volume during the acute phase (Parts 1 and 2) was significant (Pittman's test, $P = 0.01$) and positive. The correlation during remission (Part 3) was not significant. The correlation between MeImAA and 24-h urine volume during the acute phase (Part 2) could not be tested in the same way, owing to the small numbers of values. The individual correlations were positive in four and negative in two patients ($r = -0.78$ – $+0.78$). During remission (Part 3) there was no significant correlation to MeImAA.

DISCUSSION

To obtain more information about histamine metabolism in asthmatic patients, determinations of histamine metabolites (MeHi and MeImAA) have been performed. The main metabolite, 1-methyl-4-imidazoleacetic acid (MeImAA) and the intermediate metabolite, methylhistamine (MeHi) are exclusively derived from histamine and reflect the main part of the total histamine turnover in man (9, 25).

MeHi has been determined throughout the study, but MeImAA was not determined in Part 1 because of the time-consuming nature of the method. However, there was a highly significant correlation between the two metabolites, which is in agreement with the findings in an earlier study (24). Determination of Hi has been limited to Part 3 of the study because the bio-assay method was not suitable for the other parts, probably owing to the large quantities of drugs, including antihistamines, present in the urine.

The asthmatic symptoms in Parts 1 and 2 were similar in that all patients were suffering from severe attacks of intrinsic asthma, which could not be reversed by medication at home. The duration of the asthmatic symptoms

before admission, as well as the types and doses of antiasthmatic drugs taken, varied and could not be exactly determined. Because of variations in these and other factors, the first part of the study was extended to cover rather a large number of patients.

The present study has demonstrated a significant increase of the urinary excretion of MeHi in patients with acute attacks of severe intrinsic bronchial asthma compared with remission and healthy subjects. The excretion of the main metabolite, MeImAA, in six patients was also significantly higher during acute attacks compared with healthy subjects but not compared with remission in this limited number of patients.

The excretion of histamine metabolites remained high for several days after admission, roughly coinciding with the duration of the acute symptoms in most patients. An objective registration of the severity of the asthmatic symptoms was difficult to achieve but the daily doses of corticosteroids provided an indirect measure since the doses were lowered as a result of the clinical improvement.

Many studies have suggested an important role of corticosteroids in the metabolism of histamine. However, the mechanism seems to be rather complex. In some studies an increased urinary excretion of histamine has been found after administration of corticosteroids (10, 12, 14). In other studies corticosteroids have been shown to reduce the formation of histamine *in vitro* as well as *in vivo* in animals (20). This might lead to a diminished output of metabolites. Bruce et al. (5) did not find any effect of corticosteroids on urinary histamine in asthmatic patients during acute attacks. In the present study high doses of corticosteroids during the acute phase did not significantly correlate to the excretion of histamine metabolites. Neither did moderate doses of corticosteroids during remission (Part 3) cause any increase or decrease of the excretion of metabolites. For ethical reasons, the doses were not as high as those given during acute attacks. Thus there was no indication of any direct influence of cor-

ticosteroids on histamine release in asthmatic patients.

Among other factors investigated that might be related to histamine release, it was observed that the diuresis was positively and significantly correlated to the MeHi excretion during the acute phase. As the peak urine volume occurred some days after admission, this may have contributed to a delayed urinary excretion of MeHi. On the other hand, there was no correlation found between the main histamine metabolite MeImAA and diuresis.

Respiratory infection is a major clinical factor in exacerbation of intrinsic asthma. There are few data supporting an immunological mechanism by bacteria and virus (1) but a direct histamine-releasing effect of components of bacteria has been demonstrated in several studies (1, 3, 13). These data may be supported by the relatively high excretion of MeHi found in patients with signs of respiratory infection in the present study.

Smoking has been reported to give an increased output of histamine metabolites (9), and higher values in smokers were also seen in this study. The mechanism of action is unknown but direct histamine release is possible. The patients did not smoke as much as usual during the acute asthma attack, but the smoking could not be exactly quantified.

Thom et al. (23) and Mitchell et al. (16) did not find any significant rise in the excretion of histamine metabolites in the early phase of acute asthma in children and a few adults. This may be consistent with the results of the present study in which a less convincing increase of the excretion of histamine metabolites was found during the first day of investigation. The peak excretion did not occur until the fourth or fifth day after admission. We know of no obvious explanation for this late urinary excretion of histamine metabolites in acute attacks of intrinsic asthma, but a retention or delayed excretion, which has earlier been suggested for free histamine in asthma (7), may also affect the metabolites.

It may be concluded that histamine release

is increased during the acute phase of severe intrinsic asthma. The results might indicate a delayed excretion as the peak values were not obtained when the asthmatic attacks were most severe. However, what happens in the very early phase of an asthmatic attack (before admission) was not possible to evaluate in this study and is a subject for further studies. It seems reasonable that part of the increased excretion of histamine metabolites is related to the asthmatic reaction, but the present study has also shown that other factors may contribute to the increase.

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Address:

Olle Löwhagen, M.D.

Department of Allergology

First Medical Service

Sahlgrenska sjukhuset

Göteborg

Sweden

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