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Skin Reactivity to Histamine and Codeine in Unselected 9-Year-Old Children from Italy, Poland and Libya

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Key Words
Histamine skin reactivity · Codeine skin reactivity · Unselected children · International differences

Abstract
Background: Previous studies have shown that histamine skin reactivity (the dimensions of a skin wheal elicited by a prick with histamine 10 mg/ml) in unselected school children has increased in Italy during the past two decades and is higher in Italy than in Poland. Hence this variable can probably be influenced by a changing or different lifestyle. The aim of this study was to compare skin reactivity to histamine and codeine (a marker of histamine releasability from mast cells) in schoolchildren from countries with different lifestyles. ***Methods:*** Six previously unstudied unselected populations of 9-year-old schoolchildren (two each from Poland, Italy, and Libya; n = 863 subjects; 49.0% males) were pricked with two concentrations of histamine (10 and 1 mg/ml) and codeine (90 and 9 mg/ml). ***Results:*** The higher concentrations of both pharmacologic agents tested yielded significantly different wheal areas in the three countries: Poland < Italy < Libya (histamine, 11.8, 16.1 and 20.7 mm^2; codeine, 9.2, 13.2 and 16.2 mm^2; $p < 0.001$ for all comparisons). The lower concentrations elicited almost matching results. Histamine wheal areas correlated closely with areas elicited by codeine in the same individual: angular coefficients of the histamine to codeine regression lines were 0.535, Italy; 0.551, Libya; 0.612, Poland; and 0.581 for the whole population. More histamine was needed to produce a wheal in Poland than in Libya: a 20-mm^2 wheal required an injected histamine concentration of about 8.8 mg/ml in Libya, 29.5 mg/ml in Italy and 102.1 mg/ml in Poland. ***Conclusion:*** More studies are necessary to explain the observed international differences in skin histamine reactivity and their effect on the prevalence of positive allergen skin tests.

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Introduction

Allergen skin prick tests are a recognized and widely used diagnostic method to assess the atopic status of patients in clinical settings and general populations in epidemiological studies [1–4]. The result of an allergen skin prick test essentially reflects two distinct sets of events: the first set comprises a 'specific' event based mainly on mast cell degranulation caused by an interaction between an injected antigen and specific IgE antibodies on the mast cell surface, and an 'aspecific' pathway depending on the response of skin target organs (including muscle, vessels, and nerve endings) to various mediators (mainly histamine) produced by the interaction between the allergen, IgE and mast cell [5]. This aspecific pathway also depends on histamine releasability, namely the ability of mast cells to liberate histamine [6].

Through the four histamine receptors (HR 1–4) [7] histamine induces the production of several other mediators, including cytokines, interleukins, leukotrienes, prostaglandins, and substance P. Many of these in turn induce the production of further mediators including histamine itself [8, 9]. The final effect of all these substances depends on the sensitivity of end organs [5] including the 'non-adrenergic, non-cholinergic' nerve endings which on histamine stimulation can respond, via an antidromic axon response, with further local production of mediators [10].

This complex process of 'histamine skin reactivity' (in practical terms, the skin wheal dimensions elicited by a prick with histamine 10 mg/ml) can differ from one individual to another [11], possibly owing to genetic factors [12]. Our recent report that 3 histamine concentrations pricked in 3 subsequent cohorts of 9-year-old schoolchildren studied for 13 years elicited progressively larger wheals (+180% from 1983 to 1996, $p > 0.001$) [13, 14]; similar observations over 16 years [15] nevertheless show that histamine skin reactivity also undergoes environmental influences.

In another study [16], we also found that histamine skin reactivity differed in children living in Italy and Poland. This finding appeared to confirm similar findings previously reported by others (children from Sweden having larger histamine skin test responses than comparable Estonian or Polish children) [3, 17]. These international differences could be of genetic origin or depend on differences in environmental factors and lifestyle (possibly linked to a western lifestyle), or both.

Skin reactivity can also be assessed with codeine [18]. When injected into the skin, this compound activates a series of opioid cell receptors located on mast cells: when stimulated, these receptors cause mast cell degranulation and histamine liberation [19]. If the population differences in histamine skin reactivity depend mainly on mast cell histamine releasability then histamine and codeine should yield dissimilar results.

To confirm and extend previous results, in this study we studied two new cohorts of 9-year-old schoolchildren, one from Ronciglione (Italy) and the other from Starachowice (Poland) where we had conducted the 1998 study. We also studied another four new populations of schoolchildren: one in Italy (Guardea), one in Poland (Legnica) and two populations of children from a non-westernized country (Al-Azyzia and Samno in Libya). In all these children we did skin prick tests with two concentrations of histamine and codeine. In this paper we report the results of these skin prick tests done in a total of 863 children by the same two well-trained operators.

Material and Methods

The target population (about 1,000 children) consisted of all 7–9 classes of the fourth grade in the elementary schools of the chosen towns. The participation rate was 84% (80% in Italy, 90% in Poland and Libya). There were no differences in known characteristics among children from each of these cities who participated in the study or did not. We studied 863 children aged 8–10 years (mean 9.47 years) from 6 semi-rural settings. The two Italian towns were Ronciglione, a tourist resort with 30,000 inhabitants, situated near a small lake, and Guardea, a small old town with 10,000 inhabitants, situated on the Tiber valley; the Polish towns were Starachowice, a town with 59,000 inhabitants, located in a central, flat, pollution-free region, and Legnica, 100,000 inhabitants, situated in the south-west of the country, near the mountains and with some industry; the two Libyan towns were Al-Azyzia, a mainly rural center located about 40 km south of the capital Tripoli and the Mediterranean sea, 74,000 inhabitants, and Samno, a small town with 14,000 inhabitants, surrounded by large farms, 900 km from the sea, at the border of the Sahara desert.

The study protocol was approved by the Ethical Committee of the Paediatric Clinic at the University of Rome, ' La Sapienza'. The study populations consisted of unselected children from primary schools (4th-graders). Informed consent was obtained from the political and diplomatic authorities and from the parents. One week before testing, all children were asked to refrain from antihistamine medications and from inhaled or oral corticosteroids. Studies were conducted at different times of the year: in Poland in October, in Italy in November, and in Libya in January. The inside temperature of the outpatient clinics where prick tests were done was almost identical in the six geographical settings (18–22 °C; the clinics in Poland and Italy were heated). Outside daytime temperature was about 10–15 °C in Poland and Italy and 15–20 °C in Libya. Nighttime temperature was between 0 and 5 °C in all three countries. Skin prick tests were done with 2 histamine concentrations (histamine dihydrochloride 10 and 1 mg/ml), 2 codeine concentrations (codeine phosphate 90 and 9 mg/ml) and negative controls. Histamine 10 mg/ml was pricked on the

Table 1. Studied populations of unselected schoolchildren from six geographical areas in three countries

Country	Town	Number of children	Male[1]/female	Age[2], years
Italy	Ronciglione	166	78/88 (47.0)	10.04 (8.08–11.42)
	Guardea	101	50/51 (49.5)	10.07 (9.08–11.00)
Libya	Al-Azyzia	154	77/77 (50.0)	8.91 (7.42–11.42)
	Samno	180	89/91 (49.4)	9.05 (7.67–11.33)
Poland	Legnica	150	78/72 (52.0)	10.47 (8.83–12.17)
	Starachowice	112	51/61 (45.5)	9.58 (9.08–10.17)
Total		863	423/440 (49.0)	9.65 (7.42–11.42)

1 Percentage of males is shown in parentheses.
2 Mean and range in parentheses.

inner side of the left forearm, 3 cm distal to the elbow crease and histamine 1 mg/ml on the outer side, 4 cm distal to the elbow crease. Codeine (90 and 9 mg/ml) was pricked on symmetrical sites on the right forearm. Negative controls consisted of 50% glycerin in saline pricked on the outer side of the right forearm, 12 cm distal to the elbow crease, according to the International Study of Allergy and Asthma in Children (ISAAC), phase 2 protocol [20]. We used the same type of histamine and codeine in all countries (Stallergènes, Paris, France), and negative control and 1-mm tip metallic lancets (Alk-Abello, Hørsholm, Denmark). The lancet was pricked vertically into the skin through each drop of histamine, codeine and negative control, for 2 s with firm pressure, starting with histamine 10 mg/ml. A new lancet was used for each prick test. After 10 min the wheals were outlined with a thin felt-tip pen. The contours were transferred to the record sheet by means of translucent tape. The size of each wheal was measured as the mean of the longest diameter and the diameter perpendicular to it at its mid point. All tests were done by the same two well-trained operators.

In 50 children from Legnica, Poland, we measured histamine wheals twice, at 10 and 14 min after the prick test to evaluate whether the time of reading influenced the wheal size. In another 50 children from Legnica we did 2 pricks with the same histamine concentration (10 mg/ml).

All values are expressed as means ± SE. One-way analysis of variance (ANOVA) was used to compare wheals in the various towns and the post hoc Scheffé test was used for multiple comparisons. Pearson's correlation (r) was used to calculate the relationship between histamine and codeine-induced wheals. Linear regression was used to analyze the scatter plot between histamine (or codeine) concentrations and wheal area, and between histamine and codeine-induced wheals. The statistical software SPSS 9.0 for Windows was used. p values <0.05 were considered statistically significant.

Results

The repeated tests measuring histamine wheals twice at 10 and 14 min after the prick test in 50 children from Legnica to evaluate whether the time of reading influenced the wheal size yielded almost matching results. The mean difference between measures was 0.15 mm ± 0.18 mm for the 10 mg/ml concentration, and 0.05 mm ± 0.15 mm for the 1 mg/ml concentration; the coefficients of repeatability were 0.36 and 0.30 mm. In the tests using 2 pricks with the same histamine concentration (10 mg/ml) in another 50 children from Legnica wheal sizes measured 10 min after the first yielded a mean difference between measures of 0.02 ± 0.43 mm with a coefficient of repeatability of 0.87 mm.

Table 1 shows the sex and age of the six populations of unselected school children studied.

The mean wheal areas elicited by histamine (10 mg/ml) and codeine (90 mg/ml) differed in the three countries. Wheals from Polish children were half the size of those recorded in Libyan children; wheals from Italian children were of intermediate size ($p < 0.001$ for all comparisons) (table 2).

The area produced by the lower histamine (1 mg/ml) and codeine concentrations (9 mg/ml) also differed significantly in Polish children versus Italian and versus Libyan children ($p = 0.001$ for all comparisons). At these concentrations, the difference between wheals in Italian and Libyan children was not significant (table 2). Nor was a difference observed in the wheals produced by the two concentrations of the two pharmacologic agents either in boys or girls or in older and younger children in each of the three countries. The histamine and codeine wheals for the two populations from each of the three countries almost matched (fig. 1).

Pearson's test showed a strong intra-individual correlation between the size of the histamine and codeine wheals (Pearson $r = 0.650$, $p < 0.0001$). The angular coefficients of the regression lines obtained by comparing the paired

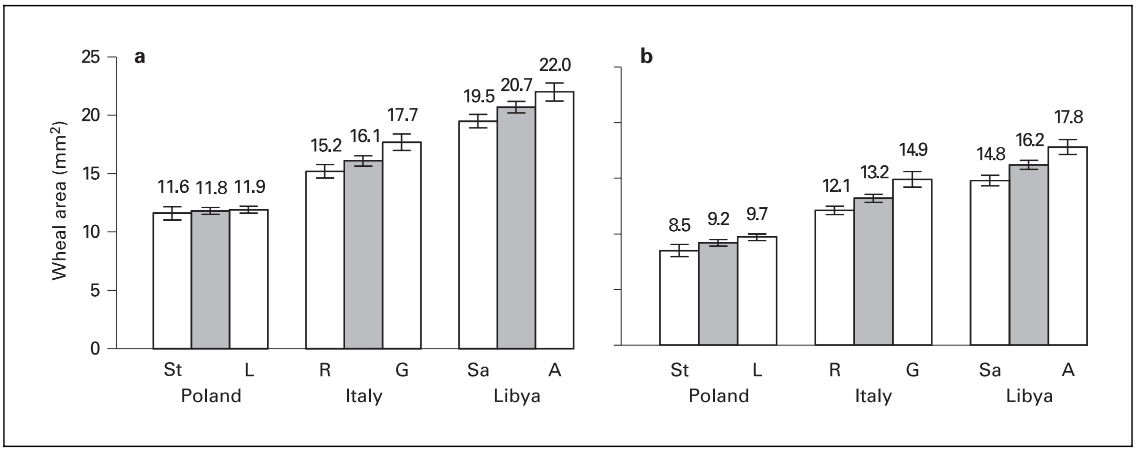

Fig. 1. Mean areas and standard errors of wheals elicited by histamine 10 mg/ml (**a**) or codeine 90 mg/ml (**b**) in each of the three countries (gray bars) and in the six populations of schoolchildren. Unlike differences between two populations from the same country, differences between countries were always significant (post hoc Scheffé test, $p < 0.001$). St = Starachowice; L = Legnica; R = Ronciglione; G = Guardea; A = Al-Azyzia; S = Samno.

Table 2. Areas of wheals (mm^2) elicited by histamine (10 and 1 mg /ml) and by codeine (90 and 9 mg/ml) in 863 unselected 9-year-old schoolchildren (262 from Poland, 267 from Italy, 334 from Libya)

		Mean[1]	± SE	Mean 95% CI	Range
Histamine 10 mg/ml	Poland	11.84	0.29	11.26–12.41	3.14–44.18
	Italy	16.13	0.45	15.25–17.02	3.98–50.27
	Libya	20.67	0.48	19.73–21.61	3.98–53.46
Histamine 1 mg/ml	Poland	5.21	0.19	4.84–5.57	0.00–17.72
	Italy	7.82	0.24	7.35–8.28	0.00–19.64
	Libya	8.18	0.23	7.74–8.63	0.00–23.76
Codeine 90 mg/ml	Poland	9.18	0.29	8.62–9.74	0.00–28.27
	Italy	13.18	0.36	12.46–13.89	3.14–47.17
	Libya	16.22	0.40	15.43–17.01	3.98–50.27
Codeine 9 mg/ml	Poland	2.40	0.17	2.06–2.73	0.00–15.90
	Italy	5.04	0.23	4.59–5.49	0.00–19.64
	Libya	5.20	0.24	4.72–5.66	0.00–28.27

[1] Mean wheals were always significantly different among countries (post hoc Scheffé test, $p < 0.001$) except for the comparison between Libya and Italy for histamine 1 mg/ml and for codeine 9 mg/ml (p = n.s.).

intra-individual values (histamine 10 mg/ml vs. codeine 90 mg/ml and histamine 1 mg/ml vs. codeine 9 mg/ml) did not differ significantly in each country from the coefficient for the whole population (0.535, Italy; 0.551, Libya; 0.612, Poland; and 0.581 for the whole population) (fig. 2).

The regression lines slopes for wheals produced in each country by the two concentrations of histamine and of codeine differed markedly (fig. 3a, b). The data sets for the two mediators yielded almost identical distribution patterns for histamine skin reactivity in the three countries. The difference in the slopes of the regression lines suggested that more histamine was required to produce a wheal in Poland than in Libya, especially to produce large-sized wheals: a 20-mm^2 wheal would require histamine pricks at a concentration of about 8.8 mg/ml in Libya, 29.5 mg/ml in Italy and 102.1 mg/ml in Poland (fig. 3a).

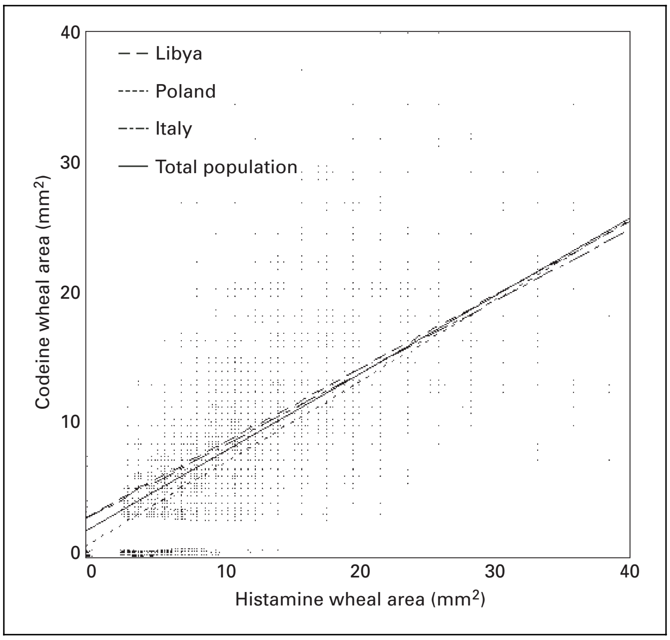

Fig. 2. Correlation lines between areas elicited by histamine 10 mg/ml and codeine 90 mg/ml and between histamine 1 mg/ml and codeine 9 mg/ml. Pearson's coefficients of correlation: total population 0.650; Poland 0.621; Italy 0.600; Libya 0.624 ($p < 0.001$ for all figures). The regression lines: total population y = 0.581x + 1.813; Poland y = 0.612x + 0.584; Italy y = 0.535x + 2.705; Libya y = 0.551x + 2.730; no significant differences were found among the angular coefficients.

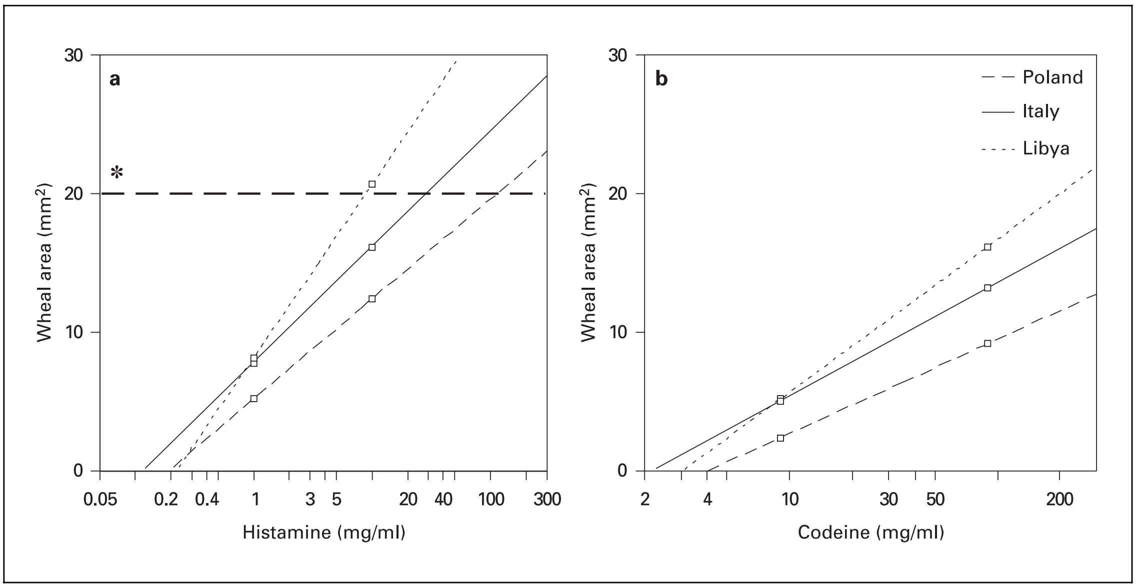

Fig. 3. a Regression lines between pricked histamine concentrations and mean skin wheal areas in the three countries: Poland y = 3.331x + 4.590; Italy y = 3.579x + 7.890; and Libya y = 5.366x + 8.314. The horizontal line (*) shows that the concentration of histamine necessary to obtain a 20-mm^2 wheal is 102.1 mg/ml in Poland, 29.5 mg/ml in Italy, and 8.8 mg/ml in Libya. **b** Regression lines between pricked codeine concentrations and mean wheal areas in the three countries: Poland y = 2.688x – 3.437; Italy y = 3.148x – 2.204; Libya y = 4.627x – 4.645.

Discussion

In this epidemiological study we confirmed and extended our previous results showing that skin wheals elicited by histamine and codeine pricked at two concentrations in unselected schoolchildren differed significantly in size in Italy, Poland and Libya. The slopes of regression lines for histamine and codeine mediator concentrations versus wheal dimensions were significantly flatter in Poland and steeper in Libya, a supposedly non-westernized country. These data imply that the amount of histamine necessary to elicit a wheal of a given dimension is significantly higher in Poland than in Libya, with Italy in the intermediate position.

Skin prick tests with codeine disclosed analogous distinctions between the three populations. The fact that similar results were obtained with histamine and codeine – which trigger the release of histamine from mast cells – implies that population differences in histamine skin reactivity did not depend on mast cell histamine releasability. Only skin mast cells (unlike those from lung, tonsils adenoids or intestine) can be activated and degranulated by means of non-immunologic stimuli e.g. opioids but also substance P, vasoactive intestinal polypeptide, somatostatin, compound 40–80, and poly-*L*-lysine [19–21].

Hence we cannot simply assume that our data on codeine skin tests hold true for mast cells located in other body parts. The matching results obtained with histamine and codeine in individuals and populations (fig. 2) suggest a similar releasability of histamine from skin mastocytes under opioid-receptor stimulation in each of the studied populations. We therefore conclude that the differences we observed in codeine skin test results in Italy, Poland and Libya arise from differences in histamine skin reactivity.

Although histamine and codeine skin prick testing has been in widespread use for many years, several variant techniques exist [18–22]. For this reason we chose the best standardized technique (the one described by ISAAC phase 2) [20]. All children were tested with an identical batch of preparations and lancets, in the same forearm site, by the same two well-trained technicians, at the same time of day and at times of the year when the three countries had a similar outside temperature. The populations were strictly unselected; the chosen sample yielded an exceedingly high participation rate (more than 90% on all occasions), and parents were asked to discontinue their children's antihistamine medications for at least a week before pricking. Histamine and codeine skin tests read in a subsample of children at 3-min intervals gave the same numerical results assuring that small inaccuracies in the time of reading (a possible event in any epidemiological procedure) did not give rise to errors. Identical prick tests repeated in the same children yielded comparable mean differences between the two measures. These preventive measures and the large number of children studied make it unlikely that technical factors affected our results.

An unexpected finding in this study was that among the three countries, Libyan children had the highest histamine reactivity. This new finding argues against our previous hypothesis that the higher histamine wheals in Swedish-Italian than in Estonian-Polish children reflected their western lifestyle. Our current results depict a more complex panorama, suggesting that genetic factors or a North to South gradient (e.g. mean year outside temperature, type of foods or spices in the diet, UVB skin exposure), or both, could be important contributing determinants of skin histamine reactivity in children.

All of the six areas studied had an acceptable and similar standard of living although socio-sanitary-hygienic conditions differed. Elucidating the possible mechanisms through which the skin of different populations (individuals) reacts differently to histamine (injected by a prick or liberated by the action of codeine on mast cells) is a complex problem. Histamine is involved in conditions ranging from neurotransmission, regulation of circulatory function and inflammatory reactions: it also exerts a potent influence on the immune response [5, 7–10]. Substance P is a mediator located in cutaneous nerve fibers [27]. It can be generated by endogenous or exogenous histamine and is an example of a positive feedback loop that amplifies the pharmacological effects of histamine. Several environmental factors can modulate the dimension of the histamine-induced wheal: for example skin inflamed by pre-treatment with sodium lauryl-sulphate shows larger histamine-elicited and substance P-elicited wheals than healthy skin [28]. Pertinent to our study is evidence that UVB light induces skin mast cell degranulation [29]. Low skin temperature, vice versa attenuates the sensitivity of the histamine skin receptor [30].

From a clinical point of view, the observed differences highlight the problems in interpreting allergen skin prick tests. The fact that in the three countries the mean wheal for the 10 mg/ml histamine concentration ranged in size from 12 to 21 mm^2 implies that in the presence of the same degree of allergic sensitization, the wheal dimensions of allergen skin prick tests could roughly double from one country to another.

In conclusion, the effects of cutaneous injections of histamine or codeine come under the influence of many mediators acting directly or through positive or negative feedback. Genetic or environmental influences interact, thus leading to an intrinsic interindividual variability in responses. In this study we provide evidence of a variability in the skin response to histamine and codeine among three countries that reaches a maximum in Libyan and a minimum in Polish children. The mechanisms underlying skin histamine reactivity and the importance of this variable in international studies using allergen skin tests to evaluate IgE sensitization deserve further investigation.

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