Quantitative skin prick and bronchial provocation tests with platinum salt

Rolf Merget, Gerhard Schultze-Werninghaus, Florian Bode, Eva-Maria Bergmann, Wolfgang Zachgo, Jürgen Meier-Sydow

Abstract
Occupational asthma due to platinum salts is a frequent disease in platinum refineries. The diagnosis is based upon a history of work related symptoms and a positive skin prick test with platinum salts. Bronchial provocation tests have not been performed in epidemiological studies because the skin test is believed to be highly specific and sensitive. As no reliable data about this issue currently exist, this study assesses the use of skin prick and bronchial provocation tests with methacholine and platinum salt in platinum refinery workers. Twenty seven of 35 workers, who were referred to our clinic with work related symptoms and nine control subjects with bronchial hyperactivity underwent a skin prick test and bronchial provocation with methacholine and platinum salt. For skin prick and bronchial provocation tests with platinum salt a $10^2$–$10^4$ mol/l hexachloroplatinic acid solution, in 10-fold dilutions was used. Four of the 27 subjects and all controls showed neither a bronchial reaction nor a skin reaction. Twenty three subjects were considered allergic to platinum salt; 22 of these showed a fall of 50% or more in specific airway conductance after inhalation of the platinum salt solution. Four workers experienced a positive bronchial reaction despite a negative skin prick test. No correlation of responsiveness to methacholine with responsiveness to platinum salt was found, but the skin prick test correlated with the bronchial reaction to platinum salt ($r = 0.50, p < 0.023, n = 22$). One dual reaction was seen in bronchial provocation tests. Side effects of both skin tests and bronchial provocation tests with platinum salt were rare and were not encountered in workers without a skin reaction to platinum salt. It is concluded that bronchial provocation tests with platinum salts should be performed on workers with work related symptoms but negative skin tests with platinum salts.

Occupational asthma, rhinitis, conjunctivitis, and eczema are common diseases in platinum refineries and catalyst production plants. The prevalence of these symptoms in cross sectional studies is considerably higher than the prevalence of a positive skin prick test with platinum salt (table 1). Thus reliable diagnostic measures are necessary to establish the causal relation between symptoms and exposure to platinum salts. For longitudinal studies quantitative assessment of sensitisation is of interest.

In platinum salt allergy in vitro data such as the radioallergosorbent test (RAST) and histamine release from basophils lack specificity. Binding rates in RAST showed some correlation with total serum IgE activity and although some authors found

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*Findings made within five years.
†Retrospective cohort analysis.
²Prevalence of upper and lower respiratory tract symptoms.
nd = Not done.

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significant differences in RAST binding rates between skin test positive subjects and controls, this test has poor sensitivity and specificity. An individual diagnosis cannot be made by means of RAST and this is also the case for histamine release from basophils with free platinum salts. 

Little information is available about histamine release with platinum salt/protein conjugates. Pepys et al. found significant histamine release with various conjugates in only one of six workers with suspected allergy to platinum salts, but not in two controls. Passive transfer of antibodies also gave conflicting results, although specificity seems high as no positive reactions were found in controls.

Thus the diagnosis of allergy to platinum salts is based on work related respiratory or cutaneous symptoms and a positive skin test. A skin prick test with platinum salt is believed to be highly specific. Little information is available about bronchial provocation tests with platinum salts. Powder inhalation without any information about the inhaled quantity was described in two early case reports. Pepys et al. performed bronchial provocation tests with 40 mg platinum salt (ammonium hexachloroplatinate, ammonium tetrachloroplatinate, and sodium hexachloroplatinate) per kg lactose powder in 16 refinery workers. Subjects inhaled the dust while shaking 250 g of this mixture. The authors described eight immediate type reactions with one dual reaction. Two subjects showed positive skin tests but negative bronchial tests. In two further cases showing negative skin prick tests with platinum salt isolated late asthmatic reactions were reported. No data about non-specific bronchial hyperreactivity were given in these studies. A control group was not included.

It was the aim of the present study to evaluate the dose response relation for a platinum salt (sodium hexachloroplatinate) in bronchial provocation tests and to define the value of skin prick and bronchial provocation tests in the diagnosis of platinum salt asthma to establish diagnostic tools for epidemiological investigations.

**Materials and methods**

**SUBJECTS**

A total of 35 workers from two platinum refineries with work related symptoms were referred to our pulmonary department for a medical opinion between February 1983 and February 1990 by the Ministry of Social Welfare. Tests were performed on average 15 (range 0–132) months after the workers had been removed from the refinery workshop. Although most workers were no longer in the refining area, 19 still had occasional contact with refinery workers or contaminated materials. Twenty seven of the 35 subjects were submitted to bronchial provocation tests with both methacholine and platinum salt. No bronchial provocation tests were performed in eight subjects (one had severe airways obstruction (forced expiratory volume in one second (FEV1) inspiratory vital capacity (IVC) 41%), three showed a mild asthmatic reaction during skin prick tests (among them another subject with severe airway obstruction), and four were not challenged for technical reasons). For controls, we investigated nine subjects with episodic asthma, bronchial hyperreactivity, and no exposure to platinum salts. Thirty three of the 35 workers (including the 27 subjects who were submitted to bronchial provocation tests) and none of the controls had any medication for at least 48 hours before the tests and neither steroids nor antihistamines for at least four weeks. Skin prick tests with platinum salt were performed on a further 100 controls with respiratory symptoms. Medication taken by these controls was not recorded. Workers and control subjects signed informed consent forms for all tests.

**CLINICAL DATA**

Data on occupational exposure time, smoking history, symptoms, and time between the onset of occupational exposure to platinum salt and the occurrence of symptoms (sensitisation period) were recorded, together with personal or family history of bronchitis, asthma, or any type of allergic disease.

**SKIN PRICK TEST**

Modified skin prick tests were performed on the volar part of the forearm with 18 common allergens (grass and tree pollens, animal dander, house dust mites, moulds (Allergopharma, Reinbek, Germany). Skin prick tests with platinum salt were performed with a stock solution of 10−2 mol/l hexachloroplatinic acid (PtCl6−2, Sigma, Munich, Germany) adjusted to pH 7.4 with 0.1 N NaOH and freshly diluted in 0.9% NaCl to 10−4 mol/l. The stock solution was stored at 4°C for not longer than four weeks. Tests were performed in duplicate. Control tests were done with NaCl (0.9%) and histamine (1 mg/ml). The histamine equivalent (the concentration of platinum salt causing a weal of the size of the histamine control or greater) was calculated with a Hewlett Packard 41C calculator from individual log dose-response curves. A positive skin prick test was defined as one with a weal diameter greater or equal to the histamine control.

**LUNG FUNCTION AND BRONCHIAL PROVOCATION TESTS**

Lung function tests (FEV1, IVC, specific airway resistance (sRaw), specific airway conductance (sGaw)) were performed using a volume constant body plethysmograph (Jaeger, Würzburg, Germany). Measuring conditions were chosen as rec-
ommended by Quanjer.\textsuperscript{19} Bronchial hyperreactivity was assessed by bronchial provocation tests with methacholine—(Aldrich, Steinheim, Germany). A methacholine stock solution of 50 mg/ml in 0.9\% NaCl was used. The stock solution was stored at 4°C for not longer than two weeks and dilutions were freshly made before tests. Bronchial provocation tests were performed between 9.00 and 12.00 am. Specific airway conductance was recorded one minute after 10 breaths of each methacholine concentration (0.5, 1, 5, 25, and 50 mg/ml). Inhalation of methacholine was from a jet nebuliser (Heyer, Bad Ems, Germany). An estimate of the amount of aerosol released from the nebuliser was made by weighing the aerosol reservoir. These measurements were used for calculation of provocation doses. The method was described by Gonsior and coworkers.\textsuperscript{20} The provocation doses causing a 50 and 35\% fall in sGaw (PD\textsubscript{0.5}sGaw and PD\textsubscript{0.35}sGaw) were calculated from the regression line between the two data points of the cumulative log dose-response curve adjacent to the 50\% or 35\% fall in sGaw by interpolation with a Hewlett Packard 41C calculator. For statistical analysis the threshold methacholine concentrations for a 50\% fall in sGaw were considered. Bronchial hyperreactivity was defined as a fall in sGaw of 50\% or more with a methacholine provocation dose of 1 mg or less.

In bronchial provocation tests with platinum, the platinum salt solution was that used in skin prick tests. The inhalation procedure was the same as for methacholine. Inhalation of platinum salt was performed with 10 breaths of 10-fold dilutions of platinum salt solutions at intervals of 15 minutes. According to non-specific reactivity and anamnestic data, bronchial provocation tests started with a platinum salt solution of $10^{-7}$ to $10^{-5}$ mol/l. Individual dose-response curves were obtained and PD\textsubscript{0.5} and PD\textsubscript{0.35}sGaw (platinum salt) were calculated as for methacholine. A positive reaction was defined as a fall in sGaw of 50\% or more with a platinum salt concentration equal to or less than $10^{-2}$ mol/l. Time-response studies were performed by measuring specific airway resistance at 0, 10, 20, 30, and 60 minutes after the inhalation of the highest platinum salt concentration. Peak flow measurements were recorded for six hours with a Mini-Wright peak flow meter (Airmed, London, England).

TOTAL SERUM IgE CONCENTRATION

IgE concentration in serum was measured with an enzyme immunoassay using anti-IgE covalently bound to paper discs (Phadezym PRIST, Pharmacia, Freiburg, Germany).

STATISTICAL ANALYSIS

Means are medians. The dose-response curve of skin prick tests and the time-response curve for bronchial provocation tests were drawn as a Box and Whisker plot with medians, maximum, and minimum values as well as upper and lower quartiles. The correlation of the parameters was determined by Spearman rank correlation analysis. Differences between the two refineries and between workers with and without actual contact with platinum salts were compared using two-tailed U tests (Wilcoxon, Mann-Whitney). For both tests a 5\% level of significance was assumed.

Results

Thirty one of the 35 workers were considered allergic to platinum salt—that is, they showed either a positive skin reaction or a positive bronchial provocation test with platinum salt. Three workers had no signs of allergy to platinum salt and one was doubtful. Table 2 gives the anamnestic data. A personal history of previous respiratory symptoms or allergic diseases was found in 13\% of subjects allergic to platinum salt. A wide variability of occupational exposure time and of the sensitisation period occurred (mean 24; range 1–264 months) without a significant difference in both refineries. Main symp-toms were rhinitis and asthma and symptoms did not differ between the refineries; 71\% of workers allergic

<table>
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<th>Personal history (%)</th>
<th>OET (months)</th>
<th>Sensitisation period (months)</th>
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Table 2 Anamnestic data. Platinum salt allergy was defined by work related symptoms, positive skin prick tests, and/or bronchial provocation tests with platinum. Personal history of the exposed group refers to those with allergic symptoms unrelated to work. Symptoms of skin (S), conjunctivitis (C), rhinitis (R), and asthma (A) are given as % of the group members. NoS = Non-smoker; ExS = ex-smoker; Smo = smoker; OET = occupational exposure time. Ranges are given in parentheses.
to platinum salt were smokers or ex-smokers; 48% of subjects allergic to platinum salt showed positive skin prick tests with standard allergens (table 3); and IgE concentration was raised (> 100 U/ml) in 50% of such workers. Only five workers had FEV₁%IVC of <65%. Thus severe airway disease was a rare finding in these platinum salt allergic workers. Allergic workers with obstructive airway disease were older (mean 49, range 41–55 years) than allergic workers with normal spirometric values (mean 32, range 19–55 years).

All workers who were not submitted to bronchial provocation tests showed a positive skin prick test with platinum salt. Four workers with severe disease or with an asthmatic reaction after skin prick tests were older (mean 54.5, range 45–55 years) than those who were challenged (mean 40, range 19–55 years). Skin reactivity to platinum salt was higher in these four workers (mean histamine equivalent reaction at mean 5.5 x 10⁻⁴ (range 1.0 x 10⁻³ - 7.2 x 10⁻²) mol/l) than in skin test positive subjects who inhaled platinum salt (mean 4.2 x 10⁻³ (range 1.0 x 10⁻⁴ - 2.6 x 10⁻³) mol/l). This subgroup of highly sensitised workers had been removed from the refinery because of severe disease but still had occasional contact with platinum salts.

Three workers showed a mild systemic reaction during skin prick tests. These subjects experienced dyspnoea, coughing, and rhinitis. Symptoms resolved without treatment. They were not submitted to bronchial provocation tests with platinum salt. Two of them had obstructive airways disease (FEV₁%IVC 37% and 41%); the third subject was highly hyperreactive (PD₉₀sGaw (methacholine) 0.39 mg).

Thirteen of the 27 subjects who underwent a skin test and bronchial provocation with methacholine and platinum salt still had occasional contact and six had regular contact with platinum salts. No differences were found in skin prick tests, bronchial provocation tests with methacholine and platinum salt, IgE concentration, or FEV₁%IVC between workers with and without contact with platinum salts. The period since the end of exposure did not correlate with lung function, IgE concentration, and reactivity to methacholine. The time since leaving the refinery workshop had a negative correlation with skin prick (r = -0.48, p < 0.014, n = 27) and bronchial provocation tests with platinum salt (r for PD₉₀sGaw = -0.53, p < 0.007, n = 27), suggesting that sensitivity to platinum salts decreases after the end of exposure. Age and occupational exposure time showed no correlation with skin reactivity and bronchial reactivity to platinum salt.

Nineteen of the 27 workers (but none of the controls (n = 109)) showed a positive skin prick test with platinum salt. One worker was doubtful; he had a weal diameter of 4 mm with the 10⁻² mol/l solution and no reactions with lower concentrations. The weal diameter of the histamine control was 7.75 mm. He experienced no 50% fall in sGaw but coughed and sneezed after inhalation of the platinum salt. The mean platinum salt concentration of subjects with positive skin tests for a histamine equivalent reaction was 4.2 x 10⁻⁵ (1.0 x 10⁻⁴ - 2.6 x 10⁻³) mol/l. Figure 1 gives the dose-response curve for the 19 subjects with positive skin prick tests with platinum salt.

With a threshold value of 1 mg methacholine, three subjects were not hyperreactive; among them were two workers considered allergic to platinum salt. These workers experienced first symptoms 28 and 38 months previously. One of them was still working in the refining area and the others had left the refinery workshop 27 months previously. Thus the lack of hyperreactivity could not be attributed to a shorter exposure period. Mean PD₉₀ sGaw (methacholine) was 0.3 (range 0.01-4.15) mg (n = 27). Figure 2 gives the methacholine concentrations causing a 50% fall in sGaw. No correlation of PD₉₀sGaw (methacholine) with PD₉₀sGaw (platinum salt) was

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Table 3  Skin prick test with standard allergens, total serum IgE, and lung function

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Ranges are given in parentheses.

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Figure 1  Box and Whisker plot of the dose-response relation for skin prick tests with platinum salt in workers with positive skin prick tests (n = 19). The dotted line represents the median of the histamine control.
found (fig 3). This was also the case with PD$_{35}$ with the threshold concentration for a 50% fall in sGaw. Also, methacholine responsiveness did not show any correlation with skin reactivity to platinum salt. Lack of correlation was also found when considering only subjects with a positive bronchial provocation test (n = 22).

Twenty two of the 27 workers had a positive bronchial provocation test with platinum salt. None of the nine controls were positive although they showed a more pronounced non-specific hyper-reactivity with a mean PD$_{50}$sGaw (methacholine) of 0-04 (range 0-02-1-09) mg. Figure 4 gives the time course of sRaw after a positive bronchial provocation test with platinum salt. Most workers experienced a fall in sGaw of 50% or more during bronchial provocation tests with platinum salt at a concentration of 10$^{-4}$ mol/l (fig 2). Mean PD$_{50}$sGaw (platinum salt) was 8-3 x 10$^{-9}$ (range 4-3 x 10$^{-10}$ - 6-2 x 10$^{-9}$) M. Four workers with positive bronchial provocation tests but negative skin prick tests with platinum salt showed a higher PD$_{50}$sGaw (platinum salt) with a mean of 2-3 x 10$^{-8}$ (range 8-9 x 10$^{-9}$ - 6-2 x 10$^{-8}$) M. Mean occupational exposure time in these workers was 41 (range 1-161) months and the mean time since leaving the refinery workshop was 9-5 (range 0-60) months. The time between the investigation and first symptoms also showed a wide range (mean 54, range 2-101 months).

**Figure 2** Threshold methacholine and platinum salt concentrations causing a fall in sGaw of 50% or more in workers with positive bronchial provocation tests with platinum salt (n = 22).

**Figure 3** Correlation of skin prick tests and bronchial provocation tests with methacholine (MCH) and platinum salt (Pt). "-PD$_{50}$" and "-His" means that no 50% fall in sGaw or no histamine equivalent reaction in skin prick test was achieved. Dots represent refinery workers (n = 27); stars are controls (n = 9). Correlation coefficients do not include control subjects.
Quantitative skin prick and bronchial provocation tests with platinum salt

The PD_{50\%} Gaw (platinum salt) showed a correlation with skin reactivity (r = 0.66, p < 0.0008, n = 27). Again, this was also the case with PD_{50\%} and the threshold value for a 50% fall in sGaw (r = 0.60 and 0.68). Correlation coefficients were lower but still significant when only subjects with a positive bronchial provocation with platinum salt were considered (r = 0.50, p < 0.023 for PD_{50\%} Gaw, n = 22).

One worker (histamine equivalent in skin prick test with platinum salt 2.8 × 10^4 mol/l, PD_{50\%} Gaw (platinum salt) of immediate reaction 4.3 × 10^{-18} M) showed a dual reaction with a clear late reaction requiring parenteral steroid therapy (fig 5). No severe immediate asthmatic responses were seen (maximum sRaw 7.5 kPa × s).

Figure 6 gives the patterns of positive reactions in skin tests and bronchial provocation tests with methacholine and platinum salt. Sixteen of 27 workers had positive reactions in all three tests. Two subjects with positive skin prick tests showed a fall in sGaw of 50% or more after inhaling the platinum salt despite a lack of hyperreactivity (PD_{50\%} Gaw (methacholine) 4.2 and 2.3 mg). Four subjects with negative skin prick tests with platinum salt had a positive bronchial provocation test with platinum salt and all of them were hyperreactive. One worker showed weak hyperreactivity to methacholine (PD_{50\%} Gaw 0.97 mg) and a positive skin prick test with platinum salt but no reaction in a bronchial provocation test with platinum salt. One worker had negative tests and was not considered allergic to platinum salts, as were three workers with bronchial hyperreactivity but negative skin tests and bronchial provocation tests with platinum salt.

Discussion

Hexachloroplatinate is the main platinum salt complex encountered in refineries and catalyst production plants. As other complexes offer no advantage, we chose the hexachloroplatinate complex for our investigation.

Thirty one of a total of 35 workers with work related respiratory symptoms were considered allergic to platinum salt—that is, they had either a positive bronchial or positive skin test reaction. One worker showed a doubtful skin reaction without a bronchial reaction. Thus workers of platinum refineries with work related symptoms have a high probability of having platinum salt allergy. As our study is not an epidemiological one, further interpretation of results is not possible.

Subjects were examined at a mean of 15 (range 0–132) months after they had left the refining area. Although reactions in skin prick and bronchial provocation tests with platinum salts decreased with increasing time since end of exposure, allergy to platinum salt could be diagnosed in 23 of 27 subjects who underwent bronchial provocation tests. Longitudinal studies are needed to determine the time course of platinum salt sensitisation after end of exposure.

The skin prick test with platinum salt is not as sensitive as it is specific. Four workers with work related respiratory symptoms and a positive bronchial provocation test with platinum salt showed no skin reactions to platinum salt. False negative skin prick tests with platinum salt were excluded because tests were performed with freshly prepared platinum salt solutions in duplicate. Negative skin tests with platinum salts and positive isolated bronchial reactions were described by Pepys and coworkers. We could not find any isolated late reaction (and only one dual reaction in a highly sensitive worker) in our subjects. This subgroup of workers with negative skin prick tests and positive bronchial provocation tests could not be identified by anamnestic data. It is not likely that the lack of skin reaction in these workers was due to a shorter period of exposure or longer absence of exposure to platinum salt. Total serum IgE concentration showed a wide variation in

Figure 4  Box and Whisker plot of the time-response relation of bronchial provocation tests with platinum salt in workers with a fall in sGaw of 50% or more (n = 22).

Figure 5  Peak flow protocol for one worker showing an immediate and clear late asthmatic reaction in bronchial provocation tests with platinum salt.
these four workers; two subjects with positive skin tests to standard allergens had raised IgE concentrations (115 and 161 U/ml); the rest, without skin reactions to standard allergens, showed normal IgE concentrations (5 and 45 U/ml). It is tempting to speculate that these subjects with negative skin reactions and positive bronchial reactions to platinum salts might show a different reaction mode, probably not mediated by IgE.

Skin prick tests with platinum salt caused mild systemic reactions not requiring treatment in three workers. As we applied a rather high quantity of platinum salt to the skin (complete dose-response curve in duplicate from $10^{-8}$ up to $10^{-2}$ mol/l), side effects might be reduced by using only one concentration or stepwise testing. For practical purposes, we recommend performing skin prick tests with a platinum salt concentration of $10^{-2}$ mol/l ($4.1 \times 10^{-3}$ g/ml). This concentration is in the range of the recommendation of Roberts who found specific skin reactions with concentrations of $10^{-3}$ to $10^{-8}$ g/ml. With the concentration of $10^{-2}$ mol/l, the maximum weal diameter was 19.5 mm and with the $10^{-3}$ mol/l solution, 12.5 mm; the doubtful reaction was not recognised and four further reactions decreased to the size of the histamine control.

Most subjects showed clear bronchial hyperreactivity. Hyperreactivity to methacholine is not a constant finding, however, in platinum salt induced asthma and is quantitatively not correlated with skin and bronchial reactivity to platinum salt. Thus quantitative assessment of bronchial hyperreactivity to methacholine is of little value for a prediction of the reaction in bronchial provocation tests.

Bronchial provocation tests with platinum salt appear to be specific as none of the controls showed any reaction. Sensitivity of bronchial provocation tests was higher than that of skin prick tests. Only one of the 23 workers who were considered allergic to platinum salt had a negative bronchial provocation. This worker with borderline hyperreactivity ($PD_{sGaw}$ (methacholine) 0.97 mg) showed no 50% fall in sGaw during a bronchial provocation test with platinum salt, but a clear clinical reaction with sneezing and coughing.

Bronchial provocation tests with platinum salt as performed in this study are not hazardous. Using stepwise increasing platinum salt concentrations, maximum airway obstruction can be kept at a moderate level. The maximum sRaw was 7.5 kPa × s with a mean maximum sRaw of 3.6 kPa × s in the group of workers with a positive bronchial reaction to platinum salts. Only one immediate reaction had to be treated by a $\beta_2$ agonist because of severe coughing. As one highly sensitised worker experienced a late asthmatic reaction, we suggest performing bronchial provocation tests in a clinical setting where emergencies can be treated adequately. We recommend a provocation dose of about $10^{-11}$ M platinum salt as the first inhalation step in highly sensitised workers, which corresponds to a concentration of $10^{-7}$ mol/l with our inhaler device. In our study only one of the 27 subjects reacted to a concentration of $10^{-6}$ mol/l; however, workers with a systemic reaction in skin tests and with obstructive airway disease were not submitted to bronchial provocation tests. Bronchial sensitivity in these subjects might be even higher. In persons with negative skin prick tests with platinum salt, a 10-fold higher platinum salt dose or concentration seems appropriate as a first step.

We have shown that work related respiratory symptoms are not predictive of platinum salt asthma. Negative skin prick tests with hexachloroplatinic acid do not exclude the disease. This has to be considered when interpreting or performing epidemiological studies concerning platinum salt asthma.

Our investigations further show that in a number of countries legal threshold values for occupational platinum salt exposure bear risks for those workers who are sensitised to platinum salt. At the threshold exposure of 2 µg/m$^3$ workers inhale about $2.0 \times 10^{-8}$ g/minute or $0.5 \times 10^{-10}$ mol/minute. This corresponds to the $PD_{sGaw}$ in bronchial provocation tests with platinum salt.

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