

Challenge of Penicillin-Allergic Volunteers with Penicillin-Contaminated Meat

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In order to obtain information about the clinical course and immunological background of possible allergic reactions due to penicillin-containing food, nine volunteers with penicillin allergy proved by case history, positive skin tests and/or positive penicilloyl-specific RAST were exposed to penicillin-contaminated pork.

For this purpose a farm pig from an inbred strain received "therapeutic" doses of benzyl procain penicillin before being slaughtered. Meat samples were taken from muscle tissues, kidney and liver and analyzed by diffusion and extraction methods. Very small amounts of penicillin were detectable in muscle tissue, whereas kidney material contained up to five times as much (0.12 mcg/g).

Except two cases which reacted with itchy sensations after ingestion of penicillin contaminated meat "à la tartare", all probands were clinically free of symptoms. Assaying penicilloyl-specific IgE antibodies by RAST during the trial, a tendency to increased levels in the serum after 2 and 24 h was noted, whereas the titers of BPO-specific IgG antibodies measured by the red cell-linked antigen-antiglobulin reaction (RCLAAR) remained unchanged. It is concluded from this study that small and hidden amounts of penicillin and its derivatives in food seldom induce anaphylactic reactions in penicillin allergic patients.

Key words: penicillin allergy; penicillin-contaminated meat.

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CLINICAL ASPECTS

As penicillin-contaminated food may still be encountered in everyday life questions arose as to how penicillin allergic subjects respond to prepared pork. For this purpose a farm pig received therapeutic doses of benzylprocainpenicillin before being slaughtered. Meat samples contained very small amounts of penicillin.

Nine volunteers proven to be allergic to penicillin by case history (in eight cases, anaphylactic reactions after penicillin treatment), by penicilloyl-specific RAST and/or by positive skin tests tolerated the meat portion prepared in the "tartare" manner. Two patients reported itchy sensations during the first 2 h after ingestion, but no anaphylactic reactions or exanthems were observed.

It is well known that in penicillin allergy reaginic antibodies (IgE) are involved, mediating reactions of the immediate type (6, 22).

Anaphylactic shock is estimated to occur in 0.015–0.04% of patients treated with penicillin, and fatal anaphylaxis in 0.0015–0.002% (11). Other IgE-mediated responses to penicillin include urticarial rashes, urticaria, angioedema, sometimes polymorphic exanthems and asthma.

Since approximately 2–5% of patients experience allergic reactions following penicillin therapy, several millions of penicillin-allergic individuals all over the world carefully avoid penicillin drugs, as readministration may cause varying degrees of inconvenience.

On the other hand, hidden contacts with penicillin often occur in everyday life (24). In order to obtain information about the clinical course and immunological background of pos-

sible reactions due to penicillin-containing meat, penicillin-allergic volunteers were exposed to prepared raw pork.

PATIENTS

Eight volunteers, four females and four males aged from 26 to 57 years and allergic to penicillin, documented by determination of the circulating penicillin-specific IgE antibodies (RAST technique) were included in this study. All of these probands had exhibited anaphylactic symptoms after treatment with different penicillins (sodium penicillin G, penicillin V, procain penicillin G) within 9 months before the challenge test procedure. A ninth patient (case No. 4), a man aged 74, had developed a maculopapular rash 7 days following treatment with amoxycillin. This patient was RAST negative, but the skin test gave a positive reaction of the delayed type to 10,000 IU sodium penicillin G i.c.

MATERIAL AND METHODS

A farm pig from an inbred strain received for a period of 3 days twice daily i.m. 1 million IU of procain penicillin G (Ilcocillin-P®, Ciba-Geigy). The animal was fed with certified antibiotic-free standard pork food. On the fourth day the animal was slaughtered (9 a.m.) and the meat cut according to standard meat market procedures. Meat samples were taken from the lumbar muscle region and the inner thigh as well as the liver and kidney. These samples were sent for analysis of their penicillin content to the Meat Hygiene Institute of the Veterinary School. The remaining meat cuts of the lumbar area were minced and taken to the II Department of Dermatology for immediate consumption.

In order to prove and examine the antibiotic activity in the sample, we used immediately upon receipt of the meat a diffusion method as well as an extraction method.

Agar diffusion test (inhibition test)

For the agar medium we used test agars from Merck® (No. 10.663 and No. 10.664) at pH values of 6.0 and 8.0. A suspension of spores from *Bacterium subtilis* (Merck Co. No. 10.613) was used on the test strain. The spore concentration was 10,000/ml. After placing the test samples of muscle, kidney and liver tissues on the test plate we analyzed the clear zone of inhibition between the sample to be examined and that of the test strain.

Extraction method

In the framework of the extraction procedure we used 50 g of muscle, and 30 g of kidney and liver, respectively. Each of these were mixed with four times the quantity of extraction fluid, consisting of one part 4 n HCl, six parts distilled H₂O and 13 parts acetone. The samples were homogenized and left overnight in the refrigerator for extraction. The extracts were then centrifuged, the extracted fluid filtered, after using 1 n NaOH for titration to pH of 6.0. A portion of the extracts was immediately tested for antibiotic contents; the remainder was tested after being autoclaved for 2 h. An agar plate with pH 6.0 was used as the test nutrient for the extraction process; 50 ml of the growth medium with the appropriate concentration of spores was poured on a large plate (13 × 25 cm, Pad Plate method according to Grady & Williams (9), so that an agar sheet of 1.7 mm thickness was obtained. This provided an increase in sensitivity of the system. The standard consisted in setting a dilution row of the autoclaved extracts with sodium penicillin G. The autoclaved extracts used as control were free of the inhibition substance.

A second series of the diffusion method as well as the extraction process was carried out on frozen meat samples. This time four different extraction fluids were used; phosphate buffer pH 6.0, NaCl-acetone titrated up to pH 3.5, HCl acidified H₂O pH 3.5 acetonitril (Merck, Art. 15) pH 5.5.

In order to examine the question of inactivation by heat, pieces (2 × 2 × 2 cm) of muscle,

liver and kidney were cooked and boiled. The diffusion rings before and after the heat exposure were examined by the above described diffusion test, using agar media at pH values of 6.0 and 8.0.

Challenge of patients

Under clinical observation and precautions all the volunteers were asked to eat a 150 g portion of raw pork prepared with salt, pepper and onions in the "beef tartare" manner. They were advised to report all possible symptoms of discomfort after 2 h, 24 h and after 14 days. At these times and before exposure, blood samples were drawn for *in vitro* assays. Patient No. 6, L.F., was checked additionally 6 h after ingestion.

Sera

After clotting at room temperature for 2 h the sera were separated and stored at -25°C until the *in vitro* tests were performed.

Radioallergosorbent test (RAST)

Circulating IgE antibodies to penicillin in the serum were assayed by the radioallergosorbent test (RAST). Benzylpenicilloyl (BPO) – and phenoxymethylpenicilloyl (PMPO) – human serum albumin coated paper discs (Phadebas RAST® Penicilloyl G + V, Pharmacia Diagnostics AB, Uppsala, Sweden) were used and tests performed with ^{125}I -Antihuman IgE (D_{E_2}) according to the instructions given by the manufacturer. The percentage bound to the human serum albumin (HSA) discs before each serum sample was subtracted from the percentage bound to the BPO-HSA or PMPO-HSA discs for the same sample. (Analyses of the values from many investigations established 0.7 as a cut-off value for differentiating positive from negative Phadebas RAST Penicilloyl results).

Serum IgE levels

The determination of the total IgE concentration in the sera was made by IgE-PRIST®

(Pharmacia Diagnostics AB, Uppsala, Sweden). The assays were performed and the results evaluated according to the manufacturer's instructions.

Red cell-linked antigen-antiglobulin reaction (RCLAAR)

Human group 0 red cells were washed three times in phosphate buffered saline (PBS), pH 7.2, and incubated with sodium penicillin G at pH 9.7 as previously reported (19). After 30 min at 37°C cells were washed four times. Equal volumes of a 2% suspension of penicilloylated red cells were then mixed with a dilution row of the human serum to be tested in glass tubes. After 30 min at room temperature the cells were washed twice and the uptake of specific antibody was measured with class-specific anti-globulin reagents in microtiter plates (17, 30). Suspensions in PBS of penicilloyl-coated red cells, which had not been incubated with human serum, were included as controls. All antiglobulin reagents were checked for specificity in hemagglutination assays performed with human erythrocytes coated with myeloma proteins by the chromium chloride method.

Skin tests

Patient No. 4 was skin tested with different antigens and different concentrations on the inner side of the forearms. The following reagents and procedures were used:

a) Benzylpenicilloyl-polylysine (PPL), first used for scratch test at a concentration of 500 nmol benzylpenicilloyl (BPO)/ml. Patients with negative results were then tested intracutaneously (0.005 ml) with 25 and 250 nmol BPO/ml.

b) Sodium penicillin G, first used for scratch test (200,000 U/ml) and followed, if negative, by successive intracutaneous injections (0.005 ml) of 10, 100 and 1000 U/ml.

c) Benzylpenicilloic acid, used for scratch and intracutaneous (0.005 ml) tests at a concentration of 5.0 mg/ml.

Table 1

Qualitative and quantitative assays of penicillin contents in fresh and frozen pork tissues. Inhibition zones in agar gels are expressed in millimeters

a. Inhibition test:

		Muscle	Liver	Kidney
Fresh material	pH 6	0	3.0	n.d.
	pH 8	0	1.7	n.d.
Frozen material	pH 6	2.0	n.d.	4.0
	pH 8	1.0	n.d.	3.0

b. Extraction method:

		Muscle	Liver	Kidney
Fresh material	pH 6	2.0	3.7	8.0
	pH 8	0	n.d.	4.0
Frozen material	pH 6	2.0	5.0	10.0
	pH 8	0	1.5	5.5

n.d. = not done; pH = pH of test agar used.

d) Ampicillin (Binotal®), used for scratch and intracutaneous (0.005 ml) tests at a concentration of 100 mg/ml.

Controls with isotonic NaCl solution and with a histamine solution (10 mg/ml for scratch and 0.1 mg/ml for intradermal tests) were included as previously described (15, 16).

Reactions were evaluated after 20 min and 48 h.

RESULTS

Qualitative and quantitative assays of penicillin contents in pork

Fresh and frozen materials gave evidence of penicillin contents in detectable amounts (Table 1a and b). Very small amounts of penicillin in muscle and liver were detectable by the inhibition and extraction methods, whereas kidney materials contained up to five-fold concentrations of penicillin. In a quantitative study (compared with standard) a content of 0.12 µg

(= 2.0 IU) penicillin per g kidney and a content of 0.06 µg per g liver tissue could be measured. Penicillin in muscle materials was detected in amounts of 0.024 to 0.04 µg/g. Cooking and boiling procedures reduced, but did not abolish, the antibiotic activity in the tissues.

Clinical data

All probands were clinically free of symptoms during the time of study except for patients 2 and 8 who reported itchy or local anaesthetic sensations during the first 2 h (Table 2). Again, in these patients no objective symptoms such as anaphylaxis, urticaria, rashes, etc. could be observed.

Results of in vitro tests

Assaying penicillin specific IgE antibodies during the course of the trial, a tendency to find raised levels in the sera of some patients after 2 and 24 h could be noted (patients 4, 5, 6, 7). These findings seem to correlate fairly well with the total IgE count levels (Table 3). Patient No. 2 exhibited a rise of total IgE, corresponding well with the time of her complaints, but no change of specific IgE antibody amount could be observed. No significant changes at all in IgE antibody levels accompanied the subjective sensations of patient No. 8. Using the RCLAAR (Table 4) penicilloyl specific IgG, but not significant amounts of specific IgM or IgA, could be detected. Again, after challenge no significant changes of the antibody titers could be observed.

DISCUSSION

The penicillins can lead to a number of antigenic determinants with high sensitizing potential. According to many investigations the major haptenic determinant in penicillin allergy is the penicilloyl group (18, 22, 29). Penicilloyl is formed either by direct reaction between penicillin and amino acid carriers or by degradation of penicillin to penicillic acid, which then forms penicilloyl conjugates. From penicillin

Table 2
Case history and symptoms of volunteers following challenge with penicillin-contaminated pork

Patient	History of penicillin allergy			Clinical reaction after exposure
	Date drug	Type of allergy	Indication for pen. treatment	
1 B.H. ♀ 37a	1974 pen G	Anaphylaxis glottis edema	Abortus	0
2 F.L. ♀ 42a	1970-procain-pen	Urticaria after 2 hours	Chronic urticaria	After 2 hours itchy sensations on abdominal skin
3 K.K. ♀ 30a	1979 pen G	Anaphylaxis	Rheumatic fever	0
4 K.A. ♂ 74a	1980 amoxycillin	Mac-pap. rash 1 day later	Nephritis	0
5 L.W. ♂ 39a	1976 pen G	Urticaria after 6 hours	Chronic erysipelas	0
6 L.F. ♂ 57a	1979 pen G	Anaphylaxis	Erysipelas	0
7 M.J. ♂ 34a	1979 pen G	Urticaria 2 h after pen V	Nephritis	0
8 M.I. ♀ 37a	1978 pen G	Anaphylaxis	Sinusitis	After 15 min "local anaes- thetic sensation" in oral mucosa, Pruritus
9 S.E. ♂ 26a	1978 pen G	Anaphylaxis	Erysipelas	0

several other antigens may be derived, collectively referred to as minor determinants.

Clinical and *in vitro* studies have shown that anaphylactic type reactions are largely or entirely mediated by IgE antibodies (1, 3, 12, 13, 15, 16, 33). Whereas penicillin allergy after medical treatment is a well-observed phenomenon, the influence of hidden amounts of penicillin in the environment on the course of allergic reactions is not entirely clear (2).

The widespread use of antibiotics for feeding, therapeutical purposes and for conservation has in some instances not only resulted in the emergence of drug-resistant coliform bacteria and staphylococci, but also in the appearance of allergic reactions after ingestion of milk and meat. The presence of penicillin in milk, due to the treatment of bovine mastitis seems to be a serious problem. Six percent of random milk samples in the USA and 4.5–5 % of samp-

les in England and Wales contained this antibiotic (7). Before being abandoned by the WHO, penicillin was used to enrich feed and as conserving agent. Penicillin-contaminated air in hospitals and factories has also been incriminated in the initiation of anaphylactic responses in hypersensitive persons (7, 23). Contaminated sterilization fluids and syringes have been responsible for serious incidents (5). It is practically impossible to eliminate all antigenic properties of penicillin by steam sterilization. It should also be remembered that some dermatophytes may produce small quantities of penicillin or penicilloyl antigens and thus initiate penicillin allergy (4).

With regard to the "trigger dose" of penicillin, even 0.000005 units of penicillin have been reported to provoke allergic responses in skin tests (24). Several other papers document anaphylactic reactions to doses of 0.01–1 unit (11,

Table 3

IgE activity to benzyl-penicilloyl (BPO) and phenoxymethyl-penicilloyl (PMPO) assayed by RAST and total IgE assayed by PRIST in nine patients at different time intervals after exposure to penicillin-containing meat

Patient		RAST and PRIST results					
		Before study	0	2 h	6 h	24 h	14 d
1 B.H.	BPO	9.53	9.6	9.8		7.8	n.d.
	PMPO	5.68	7.6	6.3		6.5	n.d.
	Total IgE	n.d.	37	25		20	n.d.
2 F.L.	BPO	1.42	1.4	1.8		2.0	1.6
	PMPO	1.14	1.3	1.3		0.7	1.3
	Total IgE	n.d	920	1500		1300	950
3 K.K.	BPO	1.0	neg.	neg.		neg.	neg.
	PMPO	1.1	neg.	0.7		neg.	neg.
	Total IgE	n.d.	15	15		15	15
4 K.A.	BPO	neg.	neg.	neg.		neg.	neg.
	PMPO	neg.	neg.	neg.		0.7	neg.
	Total IgE	nd.	60	15		130	60
5 L.W.	BPO	1.7	2.3	1.4		2.2	2.5
	PMPO	2.0	1.5	0.8		1.4	1.0
	Total IgE	n.d.	290	285		350	350
6 L.F.	BPO	30.6	28.5	37.1	30.9	23.3	23.5
	PMPO	20.4	22.3	16.9	10.1	15.2	14.3
	Total IgE	n.d.	1350	1450	1500	1550	500
7 M.J.	BPO	0.7	neg.	0.8		neg.	neg.
	PMPO	1.99	2.6	2.6		3.1	2.2
	Total IgE	n.d.	90	85		95	85
8 M.I.	BPO	2.43	3.2	2.7		3.2	3.0
	PMPO	1.45	1.7	1.3		2.1	1.8
	Total IgE	n.d.	80	75		75	75
9 S.E.	BPO	4.0	3.7	6.5		3.3	n.d.
	PMPO	12.9	12.2	10.4		11.5	n.d.
	Total IgE	n.d.	1650	1650		1450	n.d.

Calculation of RAST results was done by expressing the mean count rate a) for each individual test as percent of the mean count rate of the total activity of ¹²⁵I-Anti-IgE added, minus the value b) obtained from human serum albumin (HSA) discs with the same serum sample. PRIST results are expressed in kU/l.

21). As little as 0.003 units in milk may release symptoms after ingestion (27). Knothe (14) claimed that 0.4 units (the content of 250 ccm milk) may substantiate chronic recurrent urticaria in highly sensitive patients. Anaphylaxis to milk (31) and a soft drink (32) was observed after ingestion of about 300 and 60 IU, respectively. After the first bite of pork containing 0.31–0.45 IU penicillin G/g a penicillin allergic

butcher developed an anaphylactic shock (28). It has also been reported that anaphylaxis is less common with orally than with parenterally administered penicillins (25). In previous challenge tests six out of nine skin test positive and history positive patients reacted with either anaphylaxis, urticaria or fever (10) to penicillin doses between 2.5 × 10² and 10⁶ IU for parenteral and 4 × 250 mg for oral treat-

Table 4

Titer of BPO-reacting antibodies of different immunoglobulin classes measured by RCLAAR at different time intervals after exposure to penicillin-containing meat

Patient		0	2 h	24 h	14 d
1 B.H.	IgG	32	32	32	
	IgM	0	0	0	
	IgA	0	0	0	n.d.
2 F.L.	IgG	8	8	16	8
	IgM	0	0	0	0
	IgA	0	0	0	0
3 K.K.	IgG	512	1024	512	512
	IgM	8	8	8	8
	IgA	8	8	8	8
4 K.A.	IgG	0	0	0	0
	IgM	0	0	0	0
	IgA	0	0	0	0
5 L.W.	IgG	32	32	32	64
	IgM	2	2	2	2
	IgA	4	4	8	8
6 L.F.	IgG	64	64	64	64
	IgM	0	0	0	0
	IgA	0	0	0	0
7 M.J.	IgG	0	0	0	0
	IgM	0	0	0	0
	IgA	0	0	0	0
8 M.I.	IgG	128	128	128	128
	IgM	0	0	0	0
	IgA	2	2	2	2
9 S.E.	IgG	0	0	0	
	IgM	0	0	0	n.d.
	IgA	0	0	0	

ment. Earlier results published by Parker et al. (22) showed that 40% of his patients who had shown positive skin response to penicilloyl polysine developed allergic symptoms following penicillin therapy. In the present study nine penicillin-allergic patients proved by RAST and/or skin tests were challenged with 150 g raw pork meat containing 3–6 IU penicillin. According to the literature this dose seems to be sufficient to trigger allergic reactions. In our study none of the patients showed objective clinical signs such as anaphylactic shock, urticaria, an-

gioedema and asthma, nor were any late reactions observed. These findings show that it is unlikely that allergic reactions to penicillin are elicited by ingestion of penicillin-contaminated meat. The reason for this may be the oral route of penicillin application. In this connection a disturbed intestinal barrier and the fact that the acid-sensitive penicillin G is not absorbed very much when given perorally could influence the uptake of penicillin and/or protein-bound penicilloyl conjugates and the outcome of allergic reactions.

A second factor being involved could be the presence of blocking antibodies (IgG) circulating in the blood. The results obtained by the RCLAAR gave evidence for the penicilloyl-specific IgG only in some patients and revealed only one patient with higher amounts (a titer of 1:512 or 1024). Therefore the levels of antibodies measured argue against their protective role. Besides dose dependency and the (postulated) presence of blocking antibodies the binding affinity of the reagins is a third factor in developing allergic reactions to penicillin (20). When low-affinity reagins are present, a relatively high concentration of penicillin would be required to initiate mediator release.

We are fully aware of the facts that the small number of patients tested and the provocation test set-up do not allow exclusion of possible dangerous reactions in some individuals ("high responders") ingesting food stuff containing the same or higher concentrations of penicillin. Still, the factors discussed above and a number of non-immunological factors may contribute to the experience that in most cases hidden exposure to environmental penicillin is tolerated without symptoms.

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