

On challenge day 1, three placebo capsules (talc) were administered, one per hour. After 1 week, increasing concentrations of meloxicam were used for the challenge until a total therapeutic dose was reached. There was a 1-h interval between each dose, and if no response appeared, the next dose was administered. The doses were 1, 2, and 4.5 mg, respectively, with a total therapeutic dosage of 7.5 mg.

All substances were given in identical opaque capsules. During its execution and at the end of the test, arterial pressure and FEV₁ were monitored. Each patient was kept under observation in hospital for at least 6 h after challenge and was then asked to return or telephone to the hospital after 24 and 48 h to exclude delayed reactions.

The test was considered positive if cutaneous and mucosal manifestations (erythema and/or wheals and/or angioedema) appeared, or when respiratory symptoms or a decrease of at least 20% in the FEV₁ or hypotension developed.

The study population comprised 148 NSAID-sensitive subjects (53 males and 95 females; mean age 33.9 years [16.22 SD]; range 14–79 years). Sixty-six had experienced urticaria alone (44.6%), 34 angioedema (23%), and 48 angioedema plus urticaria (32.4%) after the ingestion of different NSAIDs. The drugs causing symptoms in these patients are shown in Table 1.

Of the 148 patients who underwent the challenge test with meloxicam, only two showed a positive test (1.35%). The first subject presented generalized urticaria associated with abdominal pain after a total dose of 3 mg of meloxicam. The second patient developed diffuse wheals and labial edema about 45 min after the administration of a total dose of 7.5 mg of meloxicam. Both patients

suffered from chronic idiopathic urticaria. No delayed reaction was observed.

None of the patients suffered adverse reactions to the placebo challenge.

This study confirms that meloxicam is a tolerable NSAID. Similar findings have been published by Quarantino et al. (2) and Košnic et al. (3).

Meloxicam is an NSAID that exerts an inhibitory effect on PGHS enzymes with a high preference for the second isoform. The exiguity of the number of positive peroral challenges may be, at least in part, explained by the selectivity of action on the PGHS-2 isoform.

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References

1. NALDI L, CONFORTI A, VENEGONI M, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999;**48**: 839–846.
2. QUARANTINO D, ROMANO A, DI FONSO M, et al. Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2000;**84**: 613–617.
3. KOŠNIC M, MUŠIČ E, MATJAZ F, SUŠKOVIČ S. Relative safety of meloxicam in NSAID-intolerant patients. *Allergy* 1998; **53**:1231–1233.

4. PAPA G, ROMANO A, DEL BONO A, et al. Floctafenine: a valid alternative in patients with adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 1997;**78**:74–78.
5. NETTIS E, DI PAOLA R, NAPOLI G, FERRANNINI A, TURSÌ A. Benzydamine: an alternative nonsteroidal anti-inflammatory drug in patients with nimesulide-induced urticaria. *Ann Allergy Asthma Immunol* 2001 (in press).

Anaphylaxis to Japanese encephalitis vaccine

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Key words: adverse reaction; anaphylaxis; gelatin; IgE; Japanese encephalitis vaccine.

• WE observed children who had systemic immediate-type reactions (cutaneous and respiratory symptoms) to Japanese encephalitis (JE) vaccine containing gelatin in amounts of 50–100 µg per dose (1). In addition, we found that vaccinees showed another pattern of cardiovascular symptoms without cutaneous symptoms after JE vaccination (2).

Physicians and vaccine manufacturers submitted 17 serum samples from vaccinees with systemic immediate-type reactions to JE vaccines, including anaphylaxis, to the National Institute of Infectious Diseases (Japan). Furthermore, some vaccine manufacturers provided us with clinical data from two vaccinees with systemic immediate-type reactions to JE vaccine. We used data from 19 vaccinees (3–14 years old; mean age ± SD, 5 years and 5 months ± 2 years and 9 months)

The incidence was 2.09 cases per million.

who showed systemic immediate-type reactions. These data were collected during a 3-year period (from April 1994 to March 1997).

Systemic immediate-type reactions to JE vaccine are classified into the following two groups, as previously described (2):

- 1) systemic cutaneous signs (e.g., systemic urticaria and angioedema) and/or respiratory symptoms (e.g., wheezing and cough) without airway obstruction
- 2) anaphylactic shock with cardiovascular symptoms (e.g., hypotension and cyanosis) without cutaneous symptoms.

These systemic reactions appeared within 1 h after vaccination.

There were nine vaccinees (aged from 3 years and 3 months to 4 years and 9 months; mean age, 4 years and 1 month) who had cutaneous and/or respiratory reactions to JE vaccine (Table 1). In 1995, we observed allergic reactions to JE vaccine for the first time. The numbers of cases exhibiting these reactions were one (0.292 per million doses) in 1995 and eight (2.09 per million doses) in 1996. Of the nine vaccinees, seven had antigelatin IgE (Immune CAP, Pharmacia, Sweden) in their sera ranging from 1.12 to 19.4 Ua/ml (mean value $\pm$ SD, 10.0 ± 5.66). These allergic reactions were probably caused by the gelatin in the vaccine. Similar adverse reactions have been reported in measles vaccine since 1993 (3). The difference in

the incidence of the adverse reactions between measles and JE vaccinees might depend on the age at which children received these vaccines. The mean age of children suffering from allergic reactions to measles vaccine was 1 year and 10 months (3) and that of those reacting to JE vaccine was 4 years.

There were 10 vaccinees (aged from 3 to 14 years; mean age, 6 years and 7 months) who experienced anaphylactic shock without cutaneous reactions to JE vaccine. In 1995, the first case of adverse reaction to JE vaccine was observed (2). There had been no previous report of adverse reactions to vaccines other than that to JE vaccine in Japan; thus, this type of anaphylactic shock without cutaneous signs after JE vaccination might be unique in vaccination. These cases of anaphylaxis were very severe, and none of the vaccinees experiencing this type of anaphylactic shock had antigelatin IgE in their sera. The immunologic mechanism for these adverse reactions has not yet been defined. In this study, we found eight vaccinees who suffered from anaphylactic shock to JE vaccine in 1996 (2.09 cases per million doses). The National Adverse Reaction Reporting System reported a similar rate of anaphylaxis to JE vaccine (4). In 1996, the incidence of severe anaphylaxis to JE vaccine in Japan was lower than the 8.13, 7.80, 8.33, and 10.3 cases per million doses of

gelatin-containing measles, rubella, mumps, and varicella vaccines, respectively (3).

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References

1. SAKAGUCHI M, YOSHIDA M, KURODA W, HARAKAMA O, INOUE S. Systemic immediate-type reactions to gelatin included in Japanese encephalitis vaccines. *Vaccine* 1997;**15**:121–122.
2. SAKAGUCHI M, INOUE S. Two patterns of systemic immediate-type reactions to Japanese encephalitis vaccines. *Vaccine* 1998;**16**:68–69.
3. SAKAGUCHI M, NAKAYAMA T, FUJITA H, TODA M, INOUE S. Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin. *Vaccine* 2000;**19**:431–436.
4. TAKAHASHI H, POOL V, TSAI TF, CHEN RT. Adverse events after Japanese encephalitis vaccination: review of post-marketing surveillance data from Japan and the United States. *Vaccine* 2000;**18**:2963–2969.

Table 1. Incidence of systemic immediate-type reactions to JE vaccine

Year	Doses (in millions)	Cutaneous and/or respiratory symptoms		Anaphylaxis without cutaneous symptoms	
		Incidence	Rate ^a	Incidence	Rate ^a
1994 ^b	4.76	0	0	0	0
1995	3.42	1 (1) ^c	0.292	2 (0) ^b	0.585
1996	3.83	8 (6)	2.09	8 (0) ^a	2.09

- ^a Number of cases per million doses of JE vaccine.
^b Japanese statistics for 1 year are collected from April to following March.
^c Number in parentheses is number of children with antigelatin IgE.