

Immediate rhinoconjunctivitis induced by metamizole: an allergic reaction?

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Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) have been frequently described (1).

Metamizole, a pyrazolone derivative with analgesic properties, frequently causes hypersensitivity reactions (2).

A 49-year-old male patient suffering from rhinitis and conjunctivitis after metamizole intake came to our observation because of need for aspirin for hypersensitivity. His clinical history gave nasal and ocular symptoms 30–60 min after the metamizole intake. As he had not taken other NSAIDs, his medical practitioner suggested the allergological evaluation before starting aspirin.

To confirm the causative role of metamizole, skin prick and intradermal tests with the drug (Novalgina® 1000 mg/2 ml, Sanofi-Aventis S.p.A.,

Milan, Italy) were carried out with negative results. Because of the described poorly dangerous adverse reactions, an oral challenge test (OCT) was performed using metamizole (Novalgina® 500 mg/ml drops). An oral tolerance test with acetylsalicylic acid (Aspro® 500 mg tablets, Bayer S.p.A., Milan, Italy) was carried out too. During the challenge tests, the respiratory functions were monitored with anterior rhinomanometry (ARM) and spirometry test upon the written informed consent. Before the OCT, the measured forced expiratory volume in 1 s (FEV1) must be at least 70% of the predicted value, and the subject must have nasal ways totally opened as assessed by ARM [total nasal resistances (*R*) of adult patients are considered as normal when lower than 0.50 Pa/cc³/s on a resistance of 150 Pa] (3)]. In addition, at the baseline, the patient must have (i) absence of nasal (rhinorrhea, sneezing) or ocular (lacrimation, eye pruritus or redness) symptoms and (ii) normal *R* after challenge with saline.

We made the OCTs with metamizole and aspirin using the provocation protocol recommended by the EAACI/GA2LEN guideline for aspirin hypersensitivity (4). We thus performed two single-blind, placebo-controlled challenge tests on two different days with a two-week interval between the two tests (for metamizole and for aspirin). For each drug on day 1, three placebo doses were administered at 1.5–2-h intervals: for metamizole, the placebo was saccharose diluted in water, for aspirin was talc inserted into inert capsules. One week later, on day 2, the drug was administered. Each successive dose was administered after 2 h if no symptoms had developed. During the test, spirometry, rhinomanometry, and arterial pressure evaluation were

monitored both before and 30 min after the drug or placebo or as soon as any symptom arose. OCT was considered as positive in case of: (i) *R* increase $\geq 100\%$ than baseline on ARM and/or (ii) symptoms like rhinitis or conjunctivitis (also in absence of rising *R*), and/or (iii) FEV1 decrease $\geq 20\%$ than the baseline. If positive reaction had occurred, the drug administration would be stopped.

The test was considered as negative in the absence of any reaction (symptomatic and/or functional) in the two protocol days after the intake of the cumulative dose of metamizole (500 mg) and aspirin (500 mg).

The metamizole OCT gave negative response on the spirometry test, and no cutaneous symptoms developed. However, patients showed rhinitis (rhinorrhea, nasal congestion) and conjunctivitis in conjunction with significant increase in nasal resistance ($R = +120$) with a sudden latency time of symptoms' development (30 min) after the first dose (Table 1). He did not show any reaction after the aspirin challenge.

Rhinoconjunctivitis reactions induced by metamizole are circumstantial (5): more frequently asthma, cutaneous, or anaphylactic reactions occur (6). This report first describes naso-ocular reactions to metamizole by oral provocation test and measured by ARM, which were not associated with other respiratory (e.g., asthma) or skin symptoms.

In the case of hypersensitivity reactions to NSAIDs, especially pyrazolones, *in vitro* diagnostics is not reliable, and the involved pathogenetic mechanism is only partially known. Himly et al. (7) developed a novel *in vitro* system to detect allergen-specific IgE that revealed an IgE-mediated mechanism in patients with adverse reactions to pyrazolones,

We investigated a rhinopathy provoked by metamizole in one patient performing skin and oral provocation tests by monitoring the nasal respiratory function by anterior rhinomanometry.

Table 1 Provocation cumulative dose, variation of total nasal resistance during the follow-up times, and symptoms in patient undergone metamizole challenge test

	Metamizole
Cumulative dose (mg)	10
R T0 ($\pm$ %)	0.25
R T1 ($\pm$ %)	0.55 (+120)
Symptoms	Rhinitis and conjunctivitis
Latency after the first dose (minutes)	30

R T0, nasal resistance at baseline; R T1, nasal resistance after the first dose.

mainly cutaneous manifestations with asthma or asthma plus rhinitis. In our patient, the negative responses to skin tests in the presence of naso-ocular symptoms and increase in $R = +120$ on ARM indicate that a metamizole metabolite may induce the IgE-mediated reaction. This hypothesis fits well with the rapidity of the onset of reaction after metamizole intake (30 min), the absence of asthma (usually present in patients who reacted to blocker of cyclooxygenase-1 agents), and tolerability to aspirin.

Asero et al. (8) showed that in patients with urticaria following a single NSAID (other than aspirin), the OCT with aspirin is safe and discriminates between single and multiple reactors according to the tolerance to aspirin or not. Here, because of the negative response to aspirin, it could be argued that not only in cases of urticaria but also in those with respiratory reactions

to a single NSAID, the provocation test using aspirin could be used to identify naso-ocular responders to one or multiple NSAIDs. The pyrazolones are drugs that may cause multifiform reactions with allergic, nonallergic, or mixed hypersensitivity which warrant further studies.

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