

Angioedema due to valsartan

J. C. Martínez Alonso, F. J. Domínguez Ortega,
J. Méndez Alcalde*, M. J. Fuentes Gonzalo

Key words: angioedema; antagonist II receptor antagonist; losartan; oral challenge test; valsartan.

Valsartan is in a class of drugs called angiotensin II receptor antagonists that prevents the constriction of blood vessels (veins and arteries). As a result, valsartan may be used alone or in combination with other anti-hypertensive agents (e.g. hydrochlorothiazide) in treating essential hypertension.

Angioedema has been found to be the result of both conventional angiotensin-converting enzyme (ACE) inhibitors (1) and, very rarely, with losartan, the other currently marketed angiotensin II receptor antagonist (2-6).

Valsartan allergy is extremely rare and there are no well-documented reports that demonstrate an allergic mechanism. In fact, there is only one clinical report of angioedema and a photosensitive pruritic rash after 3 months of therapy with valsartan without a complementary allergic study (7).

A 65-year-old woman who suffered from high blood pressure was referred to our service for angioedema palpebral after 2 weeks of therapy with valsartan (Diovan^R, Novartis Farmacéutica, Barcelona, Spain) 80 mg once a day. After discontinuing medication with valsartan and treatment with diphenhydramine and intravenous methylprednisolone, her symptoms resolved completely. She had no other drug allergy and she did not have history of familial atopy. There were no previous episodes of angioedema.

Skin prick test with common airborne and alimentary allergens was negative. The total serum immunoglobulin E (IgE) levels, the serum levels of complement fractions (C₂, C₃, C₄) and the absolute levels and activity of C₁-esterase inhibitor were normal. An oral challenge test with commercial valsartan was performed showing an immediate response with symptoms of angioedema involving lips and tongue. The reaction was resolved using subcutaneous epinephrine, antihistamines and corticosteroids in 3 h.

We performed a double-blind oral challenge test with other ACE inhibitors (captopril, enalapril), β -blockers, and calcium channel blockers, in order to find an alternative treatment, but the patient tolerated these drugs without problems. As no other cause could be identified, valsartan was probably the cause of the angioedema. There were no further episodes of angioedema in the patient after the withdrawal of the involved drug.

Until now, the pathogenic mechanism of angioedema caused by angiotensin II receptor antagonist has remained unclear. To our knowledge, we report the first case of angioedema caused by valsartan, where the immediate response in the challenge test suggest that valsartan was the drug responsible for the clinical reaction.

*Allergy unit
Hospital Virgen de la Concha
Zamora
Spain

Accepted for publication 17 October 2002
Allergy 2003; 58:367
Copyright © Blackwell Munksgaard 2003
ISSN 0105-4538

References

1. SLATER EE, MERRILL DD, GUESS HA et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988;**260**:967-970.

2. ACKER CG, GREENBERG A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995;**333**:1572.
3. SHARMA PK, YIUM JJ. Angioedema associated with angiotensin II receptor antagonist losartan. *South Med J* 1997;**90**:552-553.
4. RIVERA JO. Losartan-induced angioedema. *Ann Pharmacother* 1999;**33**:933-935.
5. CHA YJ, PEARSON VE. Angioedema due to losartan. *Ann Pharmacother* 1999;**33**:936-938.
6. RUPPRECH R, VENTE C, GRÄFE A, FUCHS T. Angioedema due to losartan. *Allergy* 1999;**94**:81-82.
7. FRYE CB, PETTYGREW TJ. Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy* 1998;**18**:866-868.

Tolerance of nimesulide in NSAID intolerant patients

A. Valero Santiago*, M. A. González-Morales,
E. Martí Guadaño, & G.E.T.N.I.A.**

Key words: nimesulide; NSAIDs-intolerance.

Nimesulide (NI) is a sulfonanilide non-steroidal anti-inflammatory drug (NSAID) that

has been shown to inhibit cyclooxygenase 2 (COX-2) with a high degree of selectivity (1).

Therefore, NI could be an alternative drug in patients with cutaneous and/or respiratory intolerance to NSAIDs (2-5). The objective of this study was to evaluate the tolerability

Nimesulide is well tolerated by 85% of the patients with NSAIDs intolerance.

**Grupo de Estudio de Tolerancia a Nimesulida en pacientes Intolerantes a AINES. Study group on tolerance of Nimesulide in patients with intolerance to NSAIDs given in Appendix.

of NI in adult patients with intolerance to NSAIDs.

One hundred and seventy-one adult patients (40.3 ± 14 years old, 63% women) were included in the study. Symptoms in their history of intolerance were cutaneous (130 patients), respiratory (58 patients) or both (17 patients). The drugs most frequently involved in intolerance reactions were aspirin (86%), pyrazolones (61%) and diclofenac (30%). All patients gave written informed consent to participate in the study which was approved by the ethics committee of the institutions involved in the study.

A simple-blind placebo-controlled oral challenge was performed on three different days in all patients: first challenge, placebo–placebo; second challenge, NI 5 and 50 mg; and third challenge, NI 50 and 150 mg. NI and placebo were administered by the oral route in the form of capsules. The interval between doses was 1 h and the time elapsing between the challenges was 7–14 days.

Arterial blood pressure, heart rate and peak expiratory flow (PEF) were measured at 0 (baseline) and 3 h after the doses. In asthmatic patients the pulmonary function was also analyzed by forced expiratory volume in 1 s (FEV₁) and PEF monitoring for 24 h.

The tolerance test was considered negative when urticaria, angioedema, rhinitis, eye symptoms and/or a decrease of 20% in FEV₁ occurred. If a delayed reaction occurred, the patient was instructed to record the symptoms in a specific form as adverse reaction, and to report them to the researcher. Patients with a positive tolerance test (no symptoms) were followed-up for 18 months.

In 25 patients (15%), the tolerance test was negative. The most frequent intolerance symptoms were: urticaria, angioedema, asthma, rhinitis, and itching. Twenty patients (80% of all NI-intolerant patients) developed symptoms with the highest dose (150 mg) of NI. These symptoms were presented isolated or in combination (Table 1).

Intolerance symptoms occurred within the first 2 h after the administration of the drug in 14 patients, within 3–6 h in eight and after 6 h in four patients.

Table 1. Intolerance symptoms after oral test with nimesulide

Nimesulide 150 mg (20 patients)	Nimesulide 50 mg (four patients)	Nimesulide 5 mg (one patient)
Urticaria (7)	Urticaria (2)	Angioedema (1)
Angioedema (3)	Asthma and rhinitis (1)	
Itching (1)	Asthma, urticaria and	
Asthma (3)	Angioedema (1)	
Rhinitis (2)		
Urticaria and Angioedema (2)		
Rhinitis and Urticaria (2)		

After 18 months of follow-up, 82 patients had used NI as anti-inflammatory treatment, 93% of them well-tolerated the drug while 7% developed urticaria and/or angioedema episodes after several doses of NI. These symptoms were similar to those developed after the administration of other NSAIDs.

Our results show that NI is well-tolerated in 85% of the patients, this percentage is similar to data published by other authors (2–5).

Nevertheless, a few studies have included a tolerance follow-up period. Quarantino et al. (6) performed a follow-up lasting for 1–3 years in patients with NSAIDs intolerance and NI tolerance, and found that 94% of patients tolerated treatment with NI, this percentage of tolerance is similar to the one that we observed (94%) in the 18 months follow-up.

In conclusion, NI shows a good tolerance profile in NSAIDs-intolerant patients. Therefore, it can be used as a safe alternative anti-inflammatory treatment in these patients.

Appendix

Al-Lergo Centre: J. Montoro, A. Malet; H. Cruz Roja de Hospitalet: E. Pinto, M. de Molina; H. Germans Trias i Pujol: M. Baltazar, L. Pau; Hospital de Manresa: R. Lleó; Instituto Dexeus: A Cisteró (Barcelona); H. General Yagüe: S. Juste (Burgos); H. San Pedro de Alcántara: S. Jiménez Timón, R. Cobo (Cáceres); Hospital Nuestra Sra. del Carmen: P. Galindo, E. Gómez Torrijos (Ciudad Real); H. Dr Josep Trueta: M. Cerdá (Gerona); Amb. Virgen de la

Cinta: L. Fernández Tavora (Huelva); H. Clínico de San Carlos: T. Robledo, C. Martínez Cocera; H. Gregorio Marañón: T. Herrero, M. Rubio; H. La Paz: C. López Serrano, P. Barranco; H. 12 de Octubre: R. Vives, G. Canto; H. Ramón y Cajal: T. Alfaya, M. Hinojosa; Fundación Jiménez Díaz: M. Lluch, J. Sastre; (Madrid); H. Nuestra Sra de la Candelaria: J.C. García Robaina (Santa Cruz de Tenerife); H. Virgen Macarena: J. Delgado, J. Conde; H. Cruz Roja: R. Gamez, A. Conejero (Sevilla); H. Juan XXIII: P. Gaig, P. García Ortega; Hospital de Reus: R. Llàtser (Tarragona); Hospital Virgen del Valle: A. Moral, C. Senent (Toledo); H. Clínico Universitario: E. Fernández Alonso, A. Peláez; H. La Fé: J. Cuellar, A. Campos (Valencia) H. Clínico Universitario: S. Lara, C. Colás (Zaragoza).

*Servicio de Neumología y Alergia
Respiratoria Hospital Clinic
Villarroel 170
08023 – Barcelona
Spain
E-mail: med000039@saludalia.com

Accepted for publication 25 November 2002
Allergy 2003; 58:367–369
Copyright © Blackwell Munksgaard 2003
ISSN 0105-4538

References

1. FAMAIEY JP. In vitro and in vivo pharmacological evidence of selective cyclooxygenase-2 inhibition by nimesulide: an overview. *Inflamm Res* 1997;**46**:437–446.
2. BIANCO S, ROBUSCHI M, PETRIGNI G, et al. Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. *Drugs* 1993;**46**:115–120.

3. ISPANO M, FONTANA A, SCIBILIA J, ORTOLANI C. Oral challenge with alternative non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol in patients intolerant of these agents. *Drugs* 1993;**46** (Suppl 1):253–256.
4. VALERO AL, GONZÁLEZ MORALES MA, MONTORO J, MALET A. Nimesulida como tratamiento alternativo en pacientes con intolerancia a antiinflamatorios no esteroides. *Rev Esp Alergol Inmunol Clín* 1998;**13**:336–338.
5. ANDRI L, SENNA GE, BETELI C, et al. Tolerability of nimesulide in aspirin-sensitive patients. *Ann Allergy* 1994;**72**:29–32.
6. QUARANTINO D, ROMANO A, PAPA G, et al. Long-term tolerability of nimesulide and acetaminophen in non-steroidal anti-inflammatory drug-intolerant patients. *Ann Allergy Asthma Immunol* 1997;**79**:47–50.