

Tolmetin: An Option for Multiple NSAID Hypersensitivity in a Preschooler

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The diagnostic process of multiple nonsteroidal anti-inflammatory drug (NSAID)-induced hypersensitivity should result with providing the patient a safe alternative. However, concomitant reactivity to acetaminophen severely limits those options in children, as no approved drug is available especially for children below the age of 12. A 3-year-old boy developed facial angioedema with ibuprofen, ketoprofen, metamizole sodium, and acetaminophen, but tolerated tolmetin sodium, which is confirmed by a challenge test. He has also used it as an antipyretic during febrile infections without any reaction. This is the first report suggesting an approved drug, tolmetin sodium, as a safe alternative for multiple NSAID-concomitant acetaminophen-reactive children.

Introduction

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) hypersensitivity in children is less prevalent than in adults and is rare, particularly in preschool age.^{1,2} When a child is found to be reactive to NSAIDs, weak inhibitors of cyclooxygenase-1 (COX-1) might be an alternative for him/her.¹ Among the weak COX-1 inhibitors, acetaminophen is the only allowed drug in preschool age. However, NSAID-hypersensitive preschoolers are also found to be 9.3-times more reactive to this medication than older children.³ Concomitant reactions to acetaminophen severely limit the options for antipyretics and anti-inflammatory treatment in children. In this report, we describe the case of a 3-year-old child reactive to all the usual antipyretics, including acetaminophen, but can safely tolerate tolmetin sodium, which is an approved NSAID for pediatric use with an antipyretic effect in this preschooler.

Case Report

A 3-year-old boy was admitted to our clinic with complaints of swelling about the lips, hands and feet, thirty minutes after receiving 100 mg of ibuprofen syrup. He first displayed the condition at age 1, when he suffered lip edema 30 min after administration of 5 mg of ketoprofen. He had also 3 more episodes of lip edema, once again 30 min after taking 5 mg of ketoprofen syrup, 2 h after ingestion of 250 mg acetaminophen (12.5 mg/kg), and 2 h after metamizole sodium injection for fever. He had no urticaria, naso-ocular, or respiratory complaints in none of the events. He has inter-

mittent allergic rhinitis since his first birthday, atopy to grass pollens, but no family history of NSAID hypersensitivity. The patient has no reported episodes of unprovoked angioedema or chronic urticaria. A diagnosis of multiple NSAID-induced angioedema was confirmed by modified oral provocation tests (Table 1). The challenges with ketoprofen, ibuprofen, metamizole sodium, and acetaminophen produced facial angioedema without urticaria. He had no alternative approved preparation for pediatric use according to the European network on drug allergy recommendations.¹ We made an oral challenge test to find a safe substitute with tolmetin sodium, for which he gave no reaction. He has also used it twice during febrile respiratory tract infections without any reaction.

Discussion

We report a 3-year-old boy developing facial angioedema with ibuprofen, ketoprofen, metamizole sodium, and acetaminophen, who tolerated tolmetin sodium. This is a case of multiple NSAID-induced angioedema that is seen in otherwise healthy subjects without chronic respiratory and/or skin disorders. The mechanism of multiple drug-induced reactions is thought to be related with the COX-1 inhibitory potential of the culprit drug.¹ The diagnostic process of multiple NSAID hypersensitivity should result in providing the patient an alternative drug.¹ However, the management of those children with concomitant reactivity to acetaminophen is not clear. In published reports, a low dose (5–10 mg/kg) of acetaminophen in conjunction with physical measures of lowering body temperature² and

TABLE 1. RESULTS OF PROVOCATION TESTS

Drug	MDD (mg/kg/day)	Doses	Reaction dose (mg/kg)	Site of angioedema	Time to reaction (after last dose)
Ibuprofen	40	10, 20, 80, 150	11.4	Lips	40 min
Ketoprofen	2	5, 20, 20	2	Cheek	9 h
Metamizole sodium	60	62.5, 125, 250, 500	40	Lips and cheek	2.5 h
Acetaminophen	60	5, 10, 50, 200	11.7	Lips	1 h
Tolmetin sodium	30	10, 50, 100, 200, 200, 140	No	No	No

Repeatedly increasing doses of medications were administered at 60-min intervals until a clinical reaction was elicited or an MSD of specified drug was achieved. The MSD was given at appropriate intervals until a maximum daily dose for weight was reached.⁹ If no reaction occurred, the MDD was continued for 2 days to exclude delayed responses.

MDD, maximum daily dose; MSD, maximum single dose.

unapproved use of selective COX-2 inhibitors^{4,5} and nimesulide⁶ were reported as possible alternatives. However, these recommended alternative drugs are approved only for children after the age of 12 years. There is no reported safe alternative recommended for preschool-age children with multiple NSAID hypersensitivity. The recommendation of tolmetin sodium as an approved drug is not reported yet.

To the best of our knowledge, this is the first presentation of the safe use of tolmetin sodium in multiple NSAID hypersensitivity in childhood. It is approved in children after the age of 2. In published reports, patients reactive to tolmetin sodium are specified as tolerable to aspirin and other potent inhibitors of COX. Although it is emphasized as causing immediate hypersensitivity reactions after interrupted dosage, neither an Ig E-mediated nor a nonallergic pathogenesis could be established.⁷

Tolmetin sodium is a pyrrole-derivative anti-inflammatory drug possessing an antipyretic effect,⁷ but the mode of action is not known exactly. It is shown that it inhibits prostaglandin synthetase *in vitro* and lowers prostaglandin E levels in man.⁸ Although it might have a potential to cause similar reactions, the absence of direct effect on COX enzyme may not be able to change the leukotriene/prostaglandin ratio dramatically, which may explain the low incidence of a clinically detectable event.

We performed oral challenge at 6 steps. This might be a limitation, because it is possible that performing challenges with 6 steps can cause desensitization. However, the history of no reaction after full drug on further use twice suggests that this is a true negativity on the drug provocation test.

This is the first report of the safe use of approved drug tolmetin sodium in a preschool child with multiple NSAIDs and concomitant acetaminophen hypersensitivity. Although it is difficult to make a general recommendation depending on one case, tolmetin sodium may be tried as an alternative antipyretic, analgesic, and anti-inflammatory drug in young children below the age of 12 with multiple NSAIDs and acetaminophen hypersensitivity.

Author Disclosure Statement

No competing financial interests exist.

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