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【 LETTERS TO THE EDITOR 】

Pharmacokinetics of Isoniazid-induced Rhabdomyolysis in a Girl

Key words: isoniazid, hydrazine, acetylhydrazine, NAT2, rhabdomyolysis

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To the Editor Komai et al. (1) described the first case of isoniazid (INH)-induced rhabdomyolysis in Japan; they speculated that mitochondrial dysfunction and adenosine triphosphate (ATP) depletion were causes of rhabdomyolysis, citing studies that suggested that INH and its metabolite hydrazine induce dysfunction of mitochondrial complexes I and II and ATP depletion (2). Two major metabolic pathways of INH are known. The main metabolic pathway of INH is through acetylation by N-acetyltransferases 2 (NAT2) followed by hydrolyzation by amidase to acetylhydrazine. The other is an alternative pathway in which INH is converted to the toxic metabolite hydrazine by amidase. Hydrazine and acetylhydrazine are further metabolized by cytochrome P450 2E1 to toxic reactants that get detoxified by glutathione-S-transferase (3). However, no studies have measured hydrazine or acetylhydrazine in patients with rhabdomyolysis. We determined the INH-induced rhabdomyolysis pathophysiology by measuring these metabolites continuously in a patient with a *NAT2* polymorphism and rhabdomyolysis due to INH overdose.

An otherwise healthy 13-year-old girl was prescribed INH 200 mg/day and pyridoxal phosphate hydrate 20 mg/day for latent tuberculosis. However, she attempted suicide by taking an overdose of INH (6,400 mg, 112 mg/kg). She developed status epilepticus lasting for 90 min and was admitted to our hospital. Table shows her blood concentrations of relevant enzymes, INH, hydrazine, and acetylhydrazine. A dose of 3,500 mg (61 mg/kg) of pyridoxal phosphate hydrate was injected to replenish pyridoxine. The peak creatine kinase level was 76,668 U/L, but it decreased because of effective renal excretion. A NAT2 gene SNP analysis revealed the presence of rs1041983 [c.282C>T (p.Tyr94)] and rs1799930 [c.590G>A (p.Arg197Gln)] alleles, and the patient was identified as an intermediate INH acetylator. The patient's general condition was good at the time of discharge (11 days after admission) without neurological sequelae or central or peripheral nerve injuries.

Polymorphisms in *NAT2* determine the INH acetylation types in humans (slow, intermediate or rapid type). Slow acetylator status is a risk factor for liver failure because hydrazine can easily be produced via an alternative pathway, but rapid or intermediate acetylator status is not a risk factor (4). This suggests that, in our patient with an intermediate acetylator status, although INH was rapidly metabolized, exposure to large INH concentrations may have induced high doses of hydrazine via the alternative pathway, thereby triggering rhabdomyolysis. High INH and hydrazine doses suppress mitochondria complex II enzymes (2, 5). Exposure to large concentrations may therefore have caused mitochondrial dysfunction and ATP depletion, thus leading to rhabdomyolysis.

The authors state that they have no Conflict of Interest (COI).

Table. Blood Concentrations of Relevant Enzymes and Isoniazid, Hydrazine, and Acetylhydrazine over Time.

	First day			Second day	Third day	Fourth day
Time of day	1:00	7:00	16:00	12:30	12:30	9:00
AST (U/L)	46	55	170	481	1,340	828
ALT (U/L)	8	9	37	119	440	571
LDH (U/L)	502	493	579	929	3,377	1,430
CK (U/L)	771	2,438	9,391	27,942	76,668	52,450
Isoniazid (μg/mL)	50.5§	-	-	<0.00	<0.00	-
Hydrazine (μg/mL)	(46.8)†	3.09§	0.05±0.01	0.04±0.00	0.01±0.00	-
Acetylhydrazine (μg/mL)	(376.4)†	36.05§	1.06±0.08	1.29±0.05	0.16±0.02	-

AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CK: creatine kinase.±denotes standard deviation.§the values only once measured: the other values are three times measured.†estimated values by calculation, Cp: blood concentrations, [Cx]: blood concentrations at x h after drug administration, kel (elimination rate constant)=[log e (C7)-log e (C16)]/(16-7 h), lnCp=lnCp0-kel·t

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