RAYNAUD'S SYNDROME IMPROVED BY THE INTRAVENOUS ADMINISTRATION OF A THROMBOXANE SYNTHETASE INHIBITOR

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Abstract: A 66-year-old man with multiple cerebral infarctions was treated with sodium ozagral; this was associated with an improvement in his Raynaud's syndrome attributable to vibration-induced white finger disease. Sodium ozagrel selectively inhibits thromboxane synthetase, reducing thromboxane A_2 (TXA_2) and also slightly increasing prostacyclin (PGI_2); this leads to vasodilatation and the inhibition of platelet aggregation. An imbalance between TXA_2 and PGI_2 caused by vascular endothelial injury is thought to cause Raynaud's phenomenon. Sodium ozagrel appears to improve the symptoms of Raynaud's syndrome by relatively increasing PGI_2, thus correcting the imbalance. Ozagrel, which currently is being used to treat cerebral thrombosis and bronchial asthma, as well as to improve vasospasm following subarachnoid hemorrhage, also may provide effective relief in patients with Raynaud's syndrome.

Index Terms

prostacyclin, Raynaud's syndrome, sodium ozagrel, thromboxane synthetase inhibitor, thromboxane A_2

INTRODUCTION

Sodium ozagrel (Xanbon® , Kissei Pharmaceutical Co., Ltd., Matsumoto, Japan) suppresses the synthesis of thromboxane A_2 (TXA_2) by selectively inhibiting TXA_2 synthetase and also promotes the simultaneous production of prostacyclin (PGI_2)[1]. At present, sodium ozagrel injections are used in the treatment of cerebral thrombosis and for improving vasospasm following a subarachnoid hemorrhage. Oral preparations are used in the treatment of bronchial asthma. We administered sodium ozagrel to a patient with cerebral thrombosis and Raynaud's syndrome, and noted an improvement in both conditions.

CASE REPORT

The patient was a 66-year-old man who at the age of 27 years first noted paroxysmal pallor of the digits of his right hand and both feet following exposure to cold. Associated symptoms included the sensations of coldness, numbness, and pain. Initially, the symptoms were observed

only in the winter, but they gradually worsened and had developed in the summer as well over the past few years. The patient was diagnosed with vibration-induced white finger disease on the basis of an occupational history. He had used a rock drill as a coal miner for 5 years from the age of 25 years and a chain saw for 3 years from the age of 35 years while engaged in forestry. He had undergone oral administration of tocopherol nicotinate and diltiazem over the past years without noticeable effects.

About 2 weeks prior to admission, he had suddenly noticed numbness and mild weakness in his right lower extremity following the consumption of alcohol. However, these symptoms resolved within a few days. On the morning of August 15, 1994, he was admitted to the hospital because of the abrupt onset of severe vertigo. The vertigo was relieved in a supine position but worsened upon sitting. The patient denied weakness or numbness in his extremities, headache, hearing loss, or tinnitus.

On admission to the hospital, he was conscious and demonstrated no neurologic deficits. His height was 165 cm and he weighed 60 kg. His blood pressure was 170/90 mm Hg and there was no difference between the two arms. His pulse was 60/min and regular, and all peripheral pulses were fully palpable. There were no signs of anemia or jaundice, and examination of the chest and abdomen was normal. No edema was observed and no abnormal bruits were audible. Pallor readily occurred in the fingers of his right hand following exposure to cold water and the cold air of an air conditioner; thus the so-called "Raynaud's phenomenon" was observed.

Urinary and hematologic values were all within normal limits (Table 1) as were chest and abdominal radiographic and electrocardiogram findings. Cervical radiography revealed no abnormalities. Plain computed tomography scans of the head, obtained on admission and the next day, showed no abnormalities. However, magnetic resonance imagings of the head obtained on day 7 revealed a large number of small infarcts in the white matter of the cerebrum (Fig. 1). Based on these findings, a diagnosis of multiple cerebral infarctions was made, and 80 mg of sodium ozagrel was administered intravenously twice a day. His vertigo began to diminish on day 3 of the treatment and had almost disappeared by day 14 at the end of the sodium ozagrel therapy. Raynaud's phenomenon was relieved after 1 week of treatment and

Table 1.

Urinalysis			BUN	12	mg/dl
protein	(−)		Scr	0.8	mg/dl
occult blood	(−)		UA	3.5	mg/dl
sugar	(−)		Na	141	mEq/l
Hematology			K	4.4	mEq/l
RBC	501×10^4	/μl	Cl^-	106	mEq/l
Hb	16.2	g/dl	TC	173	mg/dl
WBC	4000	/μl	TG	140	mg/dl
CHemistry			FBS	85	mg/dl
GOT	20	IU/l	Immunochemistry		
GPT	18	IU/l	CRP	0.8	mg/dl
LDH	291	IU/l	RA	(−)	
ALP	146	IU/l	ANA	(−)	
T-Bil	0.8	mg/dl			
Amy	70.6	mg/dl			
TP	6.7	g/dl			

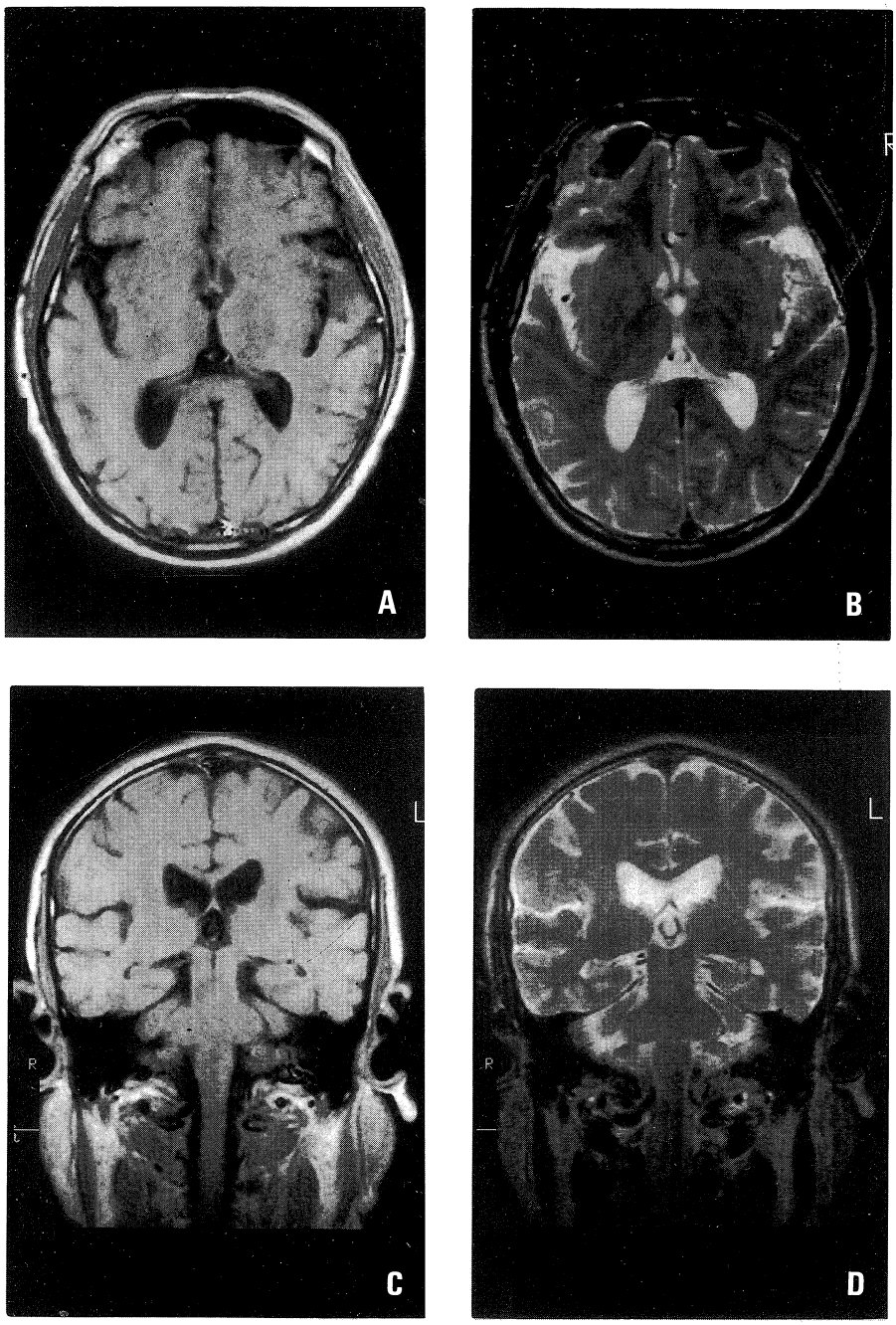

Fig. 1. Magnetic resonance images revealing multiple small infarctions.
A : T_1-weighed axial image.
B : T_2-weighed axial image.
C : T_1-weighed coronal image.
D : T_2-weighed coronal image.

could barely be induced by exposure to cold water at the end of treatment. The sodium ozagrel therapy was followed by oral aspirin. Unfortunately, however, the Raynaud's phenomenon reappeared one week after the discontinuation of oral aspirin, so the medication was switched to oral PGE_1 which provided effective relief.

DISCUSSION

Raynaund's phenomenon is a series of transient circulatory disturbances involving the periphery of the extremities that occurs following stimulation with cold and other stressors; when this phenomenon occurs secondary to a collagen vascular disease or the use of vibrating tools, it is referred to as Raynaud's syndrome. The primary and idiopathic form of this disorder is called Raynaud's disease. Raynaud's phenomenon involves transient peripheral vasoconstriction in the extremities, although platelet hyperfunction[2,3], decreased red blood cell deformability[4], and autonomic nervous system disturbances[5] also have been implicated. Although the mechanism of development has not been established, eicosanoids are thought to play a significant role in these abnormalities.

Eicosanoids are biologically active compounds that are synthesized from phospholipids through a series of reactions involving the arachidonic cascade. Due to their multiple potent actions, as well as a very rapid metabolism, eicosanoids are thought to participate in multiple local physiologic reactions. Eicosanoids are synthesized in various types of cells; PGI_2 and TXA_2 are synthesized primarily in vascular endothelial cells and platelets, respectively (Fig. 2). PGI_2 demonstrates potent vasodilating and platelet aggregation inhibiting activities; TXA_2 is a powerful vasoconstrictor and promotes platelet aggregation. Local circulation is maintained in healthy individuals by keeping a balance between these two compounds.

In patients with Raynaud's syndrome, the biosynthesis of TXA_2 is increased and may be further increased by stimulation with cold[6]. This causes an imbalance between PGI_2 and TXA_2 which is thought to be the leading cause of Raynaud's phenomenon. Several therapies have been used to try to correct this imbalance. First, PGE_1 or PGI_2 has been administered to supplement the activity of the reduced quantities of PGI_2 *in vivo*, and are effective in improving Raynaud's syndrome[7,8]. Secondly, thromboxane synthetase inhibitors (TXSIs) have been administered which should effectively treat Raynaud's syndrome since they improve the imbalance between PGI_2 and TXA_2 by depressing TXA_2 synthesis. However, earlier studies[9–11] in which patients with Raynaud's syndrome were treated with dazoxiben, a TXSI, indicated no significant improvement in either subjective clinical symptoms or objective clinical assessments. Thus, TXSIs were judged to be ineffective in the treatment of Raynaud's syndrome, and the application of dazoxiben has attracted little attention. However, in these studies, dazoxiben may not have completely inhibited thromboxane synthetase[12], so the possibility that ozagrel and other TXSIs can effectively control Raynaud's syndrome cannot be ruled out. Recently, thromboxane receptor antagonists have been developed and have been tested in Raynaud's syndrome[13].

The intravenous administration of sodium ozagrel was found to be very effective in relieving the symptoms and reducing the frequency of attacks in our patient with vibration-induced white finger disease. In this condition, the vascular endothelium of the extremities is damaged

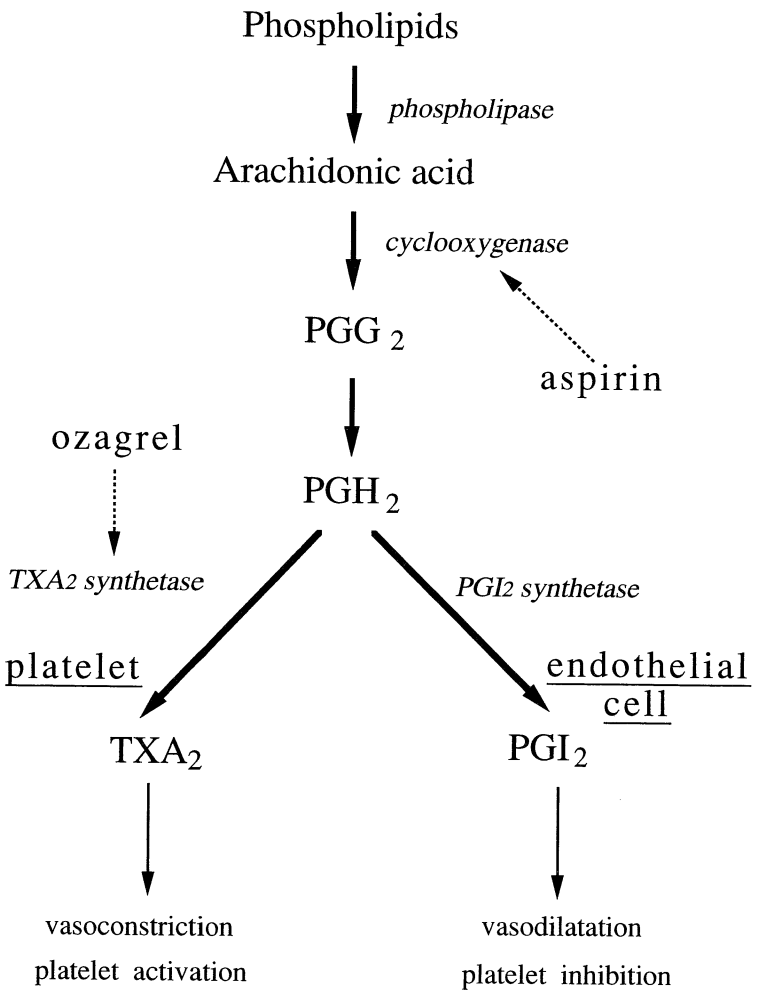

Fig. 2. Metabolic pathways of arachidonic acid.
In platelets and endothelial cells, the principal pathway for arachidonic acid metabolism is via cyclooxygenase.
Prostaglandin I_2(PGI_2)is the predominant cyclooxygenase product of endothelial cells and is a potent vasodilator and platelet inhibitor. Thromboxane A_2(TXA_2) is the predominant cyclooxygenase product formed by platelets, and is a potent vasoconstrictor and platelet agonist. Aspirin prevents the formation of both PGI_2 and TXA_2 by inhibiting the enzyme cyclooxygenase. Ozagrel selectively inhibits thromboxane synthetase and depresses TXA_2 formation without inhibiting of PGI_2 synthesis.

by excessive vibration[14], which probably causes a decrease in the PGI_2 production by vascular endothelial cells. This may induce vasoconstriction and platelet hyperfunction, leading to circulatory failure in the periphery of the extremities. Sodium ozagrel corrects the imbalance between PGI_2 and TXA_2 and improves Raynaud's syndrome. In contrast, aspirin inhibits cyclooxygenase to suppress the formation of TXA_2, but PGI_2 synthesis also is suppressed simultaneously ; this phenomenon is termed the "aspirin dilemma" and illustrates why aspirin

cannot correct the imbalance between PGI_2 and TXA_2. Aspirin was also ineffective in improving the symptoms of our patient with Raynaud's syndrome.

Various vasodilators and antiplatelet agents are now used in the treatment of Raynaud's syndrome and recently, PGE_1 and PGI_2 preparations have become available. In our patient, intravenous ozagrel was effective in treating the Raynaud's syndrome, suggesting that oral administration of this drug may have similar effects.

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