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Reevaluation of Clinical Efficacy of Peripheral Vasodilator: Ethaverine HCl*

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=國文抄錄=

末梢血管 擴張劑 Ethaverine HCl의 臨床效果의 再評價

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要 約

末梢血管擴張劑인 Ethaverine의 臨床效果는 末梢動脈疾患을 갖인 29名의 糖尿疾患者를 대상으로 二重盲檢 非交叉 方法에 依하여 硏究檢討하였다. 臨床的인 改善은 間歇性跛行症의 發生頻度를 포함하는 患者들의 病歷으로 부터 評價하였다. Ethaverine을 四週 治療後는 臨床症狀을 改善하는데 있어 僞藥에 比하여 效果가 없었다. 어쨌든 간에 Ethaverine은 僞藥보다는 血管擴張劑로서 効力이 있었다. Ethaverine에 依하여 誘發되는 血管擴張劑의 性質은 alcohol의 그것과 유사하였다. 末梢血管擴張劑를 硏究하는 새로운 臨床的 方法을 提示하였다. 下肢의 末梢血管 動脈疾患의 臨床症狀은 觸脈强度의 減少冷感 및 皮膚의 變色등을 들 수 있다. 間歇性跛行症도 수반하는 수가 있다. 血管組織에 있어서의 病變이 이같은 症狀에 先行하여 일어나며 危重한 血管不全의 立證은 血管擴張劑療法 또는 外科的 處置를 택하는데 있어서의 決定的인 要因이 된다. 만성 末梢動脈疾患이 있는 術後患者들도 次後血管擴張劑의 治療를 받아야 한다.[1] 臨床報告에 依하면 末梢血管擴張劑는 閉塞性 血管疾患에 對해서 보다는 血管痙攣性 末梢血管障害에 대해서 보다 有效하며 비교적 큰 血管床보다는 작은 毛細血管床 일때의 血管이 가장 잘 感應한다고 한다.[2]

最近에 이르러 末梢血管擴張劑의 臨床效果는 수많은 臨床硏究家들 및 臨床醫들의 硏究對象이 되고 있다. 本硏究에서 硏究者들은 血管痙攣性末梢動脈疾患을 갖인 患者들에 對한 末梢血管擴張劑로써의 Ethaverine HCl의 臨床效果를 再評價하였다. Ethaverine은 各種臨床試驗結果에 依하면 抗痙攣劑로서는 papaverine 보다도 2倍 내지 4倍정도 그 藥效가 强力하다고 한다.[3]

=Abstract=

The clinical efficacy of Ethaverine, a peripheral vasodilator, was studied according to a double-blind, non-cross over method in 29 diabetic patients with peripheral arterial disea

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ses. The clinical improvement was assessed from the history of patients including the incidence and frequency of intermitten claudication. Ethaverine, after 4 weeks of therapy, was not effective in improving clinical symptoms compared to *placebo*. Ethaverine, however, was an efective vasodilator than *placebo*. The quality of vasodilation induced by Ethaverine, was similar to that of alcohol.

A new clinical method of studying peripheral vasodilator was presented.

The clinical symptoms of peripheral vascular arterial disease in the lower extrimities include reduced intensity of palpable pulses, coldness, and discoloration of the skin. Intermittent claudication may be present. Pathologic changes in vessel architecture precede the symptoms, and recognition of impending vascular insufficiency is a determining factor in selecting vasodilating therapy or surgical management. Also, post-operative patients who have chronic peripheral vascular arterial disease may be candidates for subsequent vasodilating therapy[1]. Peripheral vasodilators, according to the series of reports, may be indicated in vasospastic peripheral vascular condition rather than an occlusive vascular disease and the vessel responds best when a relatively large vascular beds are involved rather than a small, capillary beds[2].

Recently, the clinical efficacy of peripheral vasodilators have been challanged by many clinical investigators and clinicians. In this study, we have re-evaluated the efficacy of Ethaverine HCl as peripheral vasodilator in patients with vasospastic peripheral arterial disease.

Ethaverine is claimed to be two to four times as potent a spasmolytic agent as papaverine in a variety of laboratory and clinical work[3].

METHODS AND MATERIALS

A group of referal patients were evaluated and 30 patients were admitted to this study, who met the requirments for admission. Twenty-nine patients have completed this double-blind, non-crossover study. These 29 patients, aged between 28 and 72 years old of 14 males and 15 females, were diagnosed as having diabetes mellitus, controlled well on diet, insulin or an oral anti-hyperglycemic agents.

Admission Requirements were unequivocall evidence of peripheral arterial disease of at least three months duration and a pressure difference between upper arm and ankle of 20 or more mmHg; a peripheral vascular bed reactive to an oral ingestion of 32 ml of lukewarm ethanol as domonstrated by changes observed in blood flow patterns, in ankle blood pressure, and in skin temperature of the legs; and no evidence of acute obstructive or occlusive disease of major arteries or veins. Excluded from the study were patients who has bronchial asthma; anemia; polycythemia; collagen disorders or dermatological diseases which may affect the blood flow; pregnancy; or heavy smoker or drinker.

General Outline of the Protocol is that, during the first two week observation period, each patients was given one capsule of *placebo* (identical in its appearance and teste to Ethaverine) 100 mg, three times a day prior to each meal. During the second four-week period, each patient was given either Ethaverine or its Matching *placebo*, according to the randomize code, 100 mg three times a day prior to each meal. Patients were not aware of whether he or she was taking *placebo* or Ethaverine throught the entire period of this study.

Each patient was asked to returned to the laboratory, weekly, after taking one capsule

of either the drug or *placebo* with a light breakfast for the studies of peripheral circulation. Each patient was strictly instructed not to take coffee, tea, or soft drinks containing of caffeine, or not to smoke for 24 hour period. Patients were also asked not to take any antihypertensive medications, antianginal drugs, bronchodilators, or other sympathomimetics agents for 24 hours prior to coming to the laboratory for the study.

After the patient rested for 30 minutes in a quiet room air-conditioned at 26°C, and humidity maintained at 40, a resting impedance flow of both legs was measured. Then one capsule of either active drug or *placebo* was given and the impedance flow measured for two-hours. At the end of two-hour period, 32 ml of lukewarm alcohol was given, and the flow measured for another 60 minutes.

Clinical Impression was assessed from the history of patient, changes in the skin temperature and general changes in the color of skin, changes in the ankle blood pressure, and the presence or abscence of pulsation over dorsalis pedis artery.

Impedance blood flow was measured by using an impedance plethysmograph (Systron Donnor, Palo Alto, California) and recorded on a Physiograph (Desk Model DMP-4-A, Narco Biosystems, Inc., Houston, Texas).

In the impedance system, a 120 KHz signal is introduced into an outer set of electrodes designated E_1, E_2 which defines the length of the segements and detects changes in the electrical activity that are synchronous with the heart beat (see Figure A).

Different oscillator frequencies are used in each impedance plethysmograph to prevent harmonic distortion between units. The bridge is balanced, and pulsations are recorded on a Physiograph. Following each bilateral study,

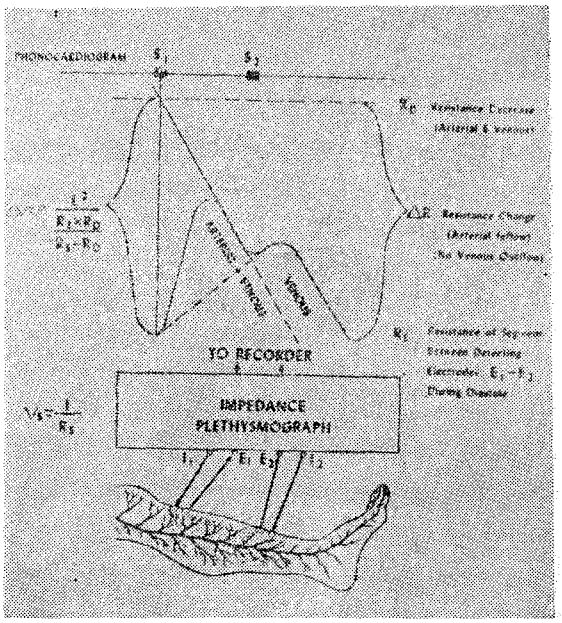

Fig. A. Impedance plethysmograph system for measuring blood pulse volume to calf segements during control and evaluation periods. Extrapolation of the pulse contour slope corrects for venous runoff and predicts the maximal amount of blood delivered to the segment during one pulse cycle.

electrode levels are switched to a substitution decade resistance circuit to balance the bridge.

A series of 0.1 to 1.0 electrical resistance standards in *ohms* are recorded and compared with the pulses. The electrical information is expressed volumetrically. Pulse volumes obtained from the leg segments during control periods are extrapolated to the begining of systole in order to correct for venous runoff, and the information is applied to a volume formula. Each pulse volume multiplied by the pulse rate expressed blood flow to the leg segments, and the minute volume is divided by leg volume and expressed per 100 ml of tissue blood flow.

RESULTS

Upon breaking the double blind code, it was

found that 8 females and 7 males took *placebo* during the second 4-week trial period, and 7 females 7 males were receiving Ethaverine.

An over-all improvement in *"clinical impression"* was observed in 9 out of 14 patients receiving Ethaverine (64.2%), and a similar improvement was found in 7 out of 15 patients on *placebo* (46.7%), and the difference between Ethaverine and *placebo* was not statistically significant.

Based on the blood flow measured by impedance plethysmograph, Ethaverine caused a marked increase in blood flow in 9 out of 14 patients, while *placebo* caused a moderate degree of vasodilation in 5 out of 14 patients, and the difference between Ethaverine and *placebo* was statistically significant ($p<0.05$ by Wilcoxon Matched signed ranks test).

The resting blood flow measurements during the second 4-week Ethaverine or *placebo* trial period, was plotted against the controls in each patient (Figure 1). Ethaverine caused a marked rise in blood flow compared to the controls, and against the placebo effect.

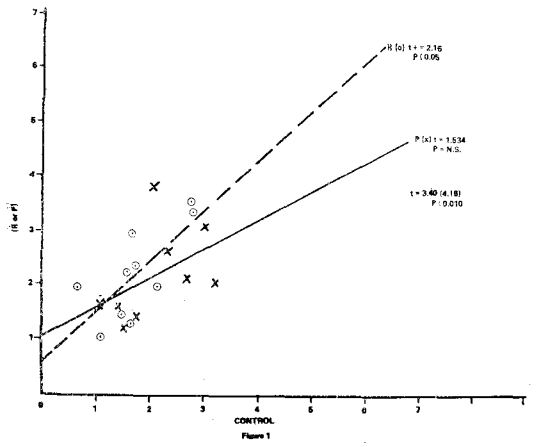

Fig. 1. The resting blood flow of lower limbs before (Control and after taking Ethaverine (Rx) or *placebo* (P) were compared. The resting flow was increased after the drug (Rx) compared to the controls.

The degree of vasodilation induced by Ethaverine was similar to that of induced by alcohol (Figure 2). The degree of vasodilation induced by Ethaverine was linearly related to the flow after alcohol ingestion and the slope was 0.98, almost of 1.0. No vasodilation, but actually reduced resting flows, were observed with *placebo* as compared to the flows after the alcohol (Figure 2, Table 1).

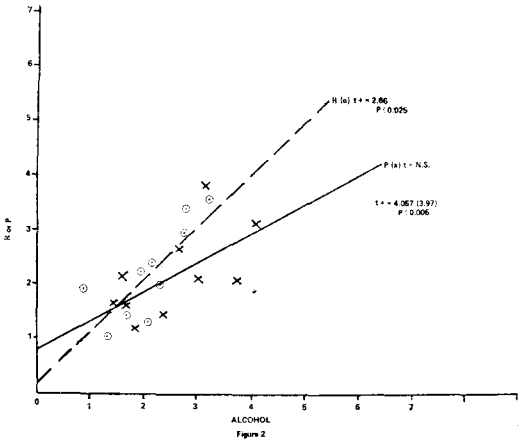

Fig. 2. The resting flow after Ethaverine (Rx) or *placebo* (P) was compared to the flows following ingestion of alcohol. The vasodilation induced by Ethaverine and alcohol was similar in that the slope of correlation was 0.98.

In order to find whether the observed vasodilation after Ethaverine was qualitatively similar to that of alcohol, after the measurements of resting blood flow, the drug or *placebo* was given to each patient together with 32ml of lukewarm alcohol and the flow remeasured (see Methods & Marterials). The oretically, if the vasodilation has been maximally achieved by Ethaver then no additional vasodilation may be induced by ingestion of alcohol and Ethaverine. However, if the vasodilation induced by the drug or *placebo* was qualitatively different from that of vasodilation induced by alcohol, then an additional

Table 1. Circulatory responses to alcohol, ethaverine and its placebo (ml/min/100 gm of Leg Muscle)

Group	Control	Alcohol	Drug or placebo	Drug or placebo+alcohol
Ehtaverine	1.97±0.188	2.10±0.161	2.13±0.201	2.26±0.198
	100%	115.9±6.79*	125.2±10.39*	115.7±7.25+
Placebo	2.38±0.236	2.56±0.280	2.18±0.241	2.76±0.260
	100%	130.1±9.76*	105.9±11.85	129.0±6.63+

* Statistically significant (p less than 0.05 or less)
+ The percental value calculated against drug or placebo as 100%

increment in blood flow should be recorded by taking both the drug or *placebo* and alcohol.

After *placebo* and alcohol, a marked vasodilation was observed (Table 1, Figure 3), while no additional vasodilation was observed after Ethaverine.

No severe or unsual side effects were observed during the four-week study on Ethaverine or *placebo*.

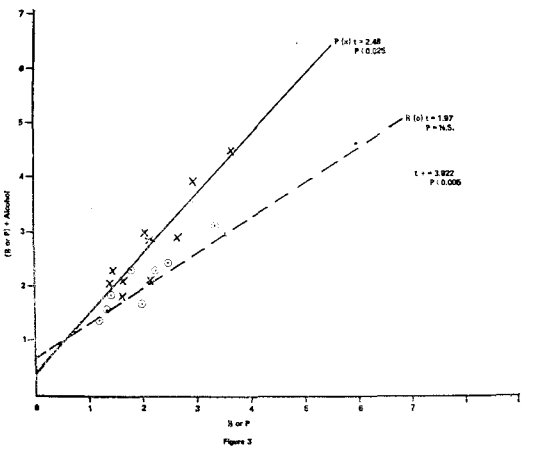

Fig. 3. An additive effect between Ethaverine and alcohol, of *placebo* and alcohol in each case, was compared against the effect of Ethaverine (Rx) or *placebo* alone. No further vasodilation was observed after Ethaverine and alcohol, compared to Ethaverine alone.

DISCUSSION

The circulation in the upper and lower limbs of man is so regulated that at all times it is adequate for local tissue needs and consistent with the requirements of the body as a whole. These two governing influences are frequently opposed and to maintain a correct balance a complex vasomotor mechanism is required. This mechanism consists of the blood vessels themselves, and those factors such as nervous and humoral agents which regulate blood vessel activity. However, in diabetic patients, usually, atherosclerosis and generalized arteriosclerosis comonly occur. Patients with diabetes tend to have hypercholesterolemia and other evidences of a distrubed fat metabolism. In these patients, clinical symptoms and signs of peripheral vascular circulatory failures and 'intermittent claudication' may occur often.

Since the peripheral circulation is regulated by endogenous as well as exogenous factors including environmental factors, evaluation of clinical efficacy of vasodilator becomes somewhat difficult. Perhaps, the method described herewith, may be sufficient to conduct such a study in man.

Based on our data, the clinical impression including the incidences and frequencies of intermittent claudication, was not the best method of evaluating the clinical efficacy of peripheral vasodilators. Nevetherless, the authorities including the Food and Drug Administration of U.S. government insist on showing the clinical improvements after taking vaso-

dilators. In this sense, then Ethaverine was not an effective vasodilator.

As a vasodilator, however, Ethaverine was as effective as lukewarm alcohol. It has been reported that alcohol was a potent peripheral vasodilator[4]. In our double-blind, controlled clinical study, Ethaverine was better than *placebo* in inducing vasodilation in diabetic patients with vascular diseases.

Probably, inorder to improve clinical symptoms of peripheral vascular 'insufficiency', Ethaverine most be given over longer period of time and 4-week trial period, applied in this study, was insufficient in period of time.

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