Pharmacological Properties of Traditional Medicines. XXIV.1) Classification of Antiasthmatics Based on Constitutional Predispositions

Dan YUAN, a Ken-ichi KOMATSU, a Hideaki TAN, a Zheng CUI, b and Yoshihiro KANO* a

Department of Kampo Medicinal Science, Hokkaido College of Pharmacy, 7–1 Katsurahaka-cho, Otaru 047–0264, a Japan and Department of Pharmacognosy, Shenyang Pharmaceutical University, b 103 Wenhua Road, Shenyang 110015, China.

Received June 12, 1998; accepted August 4, 1998

It is commonly accepted that bronchial asthma or rhinitis accompanies disorders in body fluids and body temperature. The effects of ephedrine and the traditional antiasthmatics “Makyo-kanseki-to” and “Goko-to” were therefore studied on such constitutional predispositions as insensible perspiration and body temperature. Ephedrine markedly increased body temperature and exhibited a strong increased action on respiratory insensible perspiration, whereas Makyo-kanseki-to and Goko-to not only prevented the elevation of body temperature, but also increased respiratory insensible perspiration following the reduction of non-evaporative heat loss from the body surface. Thus, the diagnostic criteria of these two medicines used to treat hot-type asthma or dry cough were experimentally determined. The results also suggest that there is a great possibility that the administration of antiasthmatics may elicit side effects or make diseases worse unless their actions on constitutional predispositions are taken into account, such as body temperature and body fluids.

Key words bronchial asthma; body temperature; heat-fluid transformation; insensible perspiration; traditional medicine

Environmental factors such as seasonal or diurnal variations in atmospheric temperature and humidity, namely, the hot or the cold and the damp or the dry, are believed to allow development of such diseases as bronchial asthma, rhinitis, and rheumatoid arthritis.2) The unidentified clinical syndromes of headache, vertigo and chill of extremities are also deeply affected by these factors.3) There is a close correlation between these diseases or symptoms and the disorders in body temperature and the distribution of body fluids.4) Except for urination, water discharge from the body depends to a considerable extent upon insensible perspiration, by which about 40% of the total amount of water is evaporated per day when the body is in a normal condition.5)6) Insensible perspiration is also closely associated with body temperature, by which about 1/4 of the daily heat from metabolism and so on is lost in the form of gasification. It is strongly influenced by the atmospheric temperature and humidity as well.7) 8) If thermoregulation does not coordinate with the changes in the atmospheric temperature or humidity, its amount is affected and the distribution of body fluids will be disordered. In a cold and damp condition, for example, it is difficult for the function of insensible perspiration to be performed regularly, which gives rise to a predisposition to edema. In turn, the physico-chemical reactions or biological processes in extracellular or intracellular fluids are out of order. As a result, the body is in a non-physiological condition, which is, according to the traditional medical theory, thought to be the basic cause of such diseases or symptoms as mentioned above.9) Similarly, an excess of heat production causes an increase in insensible perspiration to maintain thermal homeostasis, bringing about a deficiency of body fluids and eliciting thirst or over-drinking.10)1) The cellular environment in a condition of condensed body fluids results in a tendency to dehydration, the opposite of edema, which is also thought to cause the above-mentioned diseases or symptoms in traditional medical theory. These may provide a theoretical explanation for the differences between the symptoms of upper respiratory diseases, such as dry cough and wet cough. Of course, the predisposition towards to edema or dehydration may be only a prelude to clinical findings. Such cellular environments are widely accepted to be basic factors in the occurrence of abnormal immune responses that result in asthma or rheumatoid arthritis.12) Thus, an ideal treatment should aim at improving the ability to maintain the cellular environments, rather than preventing immune response or employing antihistamimics. In fact, it has been proved that traditional medicines have a poor antihistaminic effect or little direct immunodepressive effect. Even though their antihistaminic effect was confirmed by in vitro experiments, their potency has not been clinically assessed.12) This suggests that traditional medicines may exert their influence in the basic stage of the immune response.13) These views are consistent with the clinical report that traditional medicines may effect a radical cure of the above-mentioned diseases or symptoms thus freeing patients from the necessity of their administration.2)

Our studies on the traditional medicines used to treat bronchial asthma and rhinitis therefore centered on their effects on constitutional predispositions, such as body temperature and insensible perspiration. A new experimental device was developed to measure body temperature (Tr), respiratory and cutaneous evaporative water loss (REW and CEWL), and dry heat loss (non-evaporative heat loss, DHL) from skin and respiratory organs (CDHL and RDHL) in rats. The results with the device agreed to the classical dissertations or clinical reports on the adaptation syndromes and contraindications of these traditional medicines. It is useful in evaluating the effects of traditional medicines on body temperature and insensible perspiration, as reported previously.13)

In this paper, the dose-response relationships of Makyo-kanseki-to (MKK, 麻黃甘石湯) and Goko-to (GKT, 五虎湯) were investigated in detail using our method together with the positive control drug, ephedrine (Eph), in an attempt to determine their actions on constitutional predispositions.

MATERIALS AND METHODS

Drugs MKK [Ephedra Herb (麻 黃) 4.0 g, Apricot Kernel (杏仁) 4.0 g, Licorice (甘草) 2.0 g, Gypsum (石] © 1998 Pharmaceutical Society of Japan

* To whom correspondence should be addressed.
Effects on Insensible Perspiration and Tr

For comparative analysis, MKK was orally given at the dose of 127.22, 254.45 and 508.90 mg/kg, respectively, which corresponded to positive control Eph of 2.00, 4.00 and 8.00 mg/kg. Similarly, oral doses of GKT were 164.06, 328.12 and 656.25 mg/kg, which were the respective equivalents of Eph of 2.00, 4.00 and 8.00 mg/kg. The results are shown in Figs. 1—5.

First, there was a significant increase in REWL when either Eph, MKK or GKT was given to the animals, as compared to that of saline control. All the effects exhibited the dose-dependence (Fig. 1). The average increased ratio of the traditional medicines was less than that of the same content of Eph (Table 1), but without significance. RDHL showed the different results from REWL. It was observed that Eph markedly increased RDHL, which was depressed in the administration of MKK or GKT. At a low dose of MKK, RDHL was significantly decreased by 10%, showing no difference at the intermediate dose and a 15% significant increase at the high dose. GKT exhibited a similar tendency to MKK, whereas significant differences from the saline control were not confirmed (Fig. 3).

Second, notable actions of these medicines on CDHL were apparent in spite of no clear effects on CEWL being seen. Eph showed only a slight tendency to increase CDHL but the difference from saline control was not significant. Contrary to Eph, a decrease in ratio of about 10% in CDHL was statistically confirmed when rats were given MKK or GKT in comparison to those of saline control. Moreover, these depressant actions were not only of dose-dependence but also of statistical significance compared to those of Eph (Figs. 2 and 4).

Third, a noticeable phenomenon concerning Tr was that
there was a distinguishable action of MKK or GKT from that of Eph. The Tr of the animals given Eph dose-dependently increased with a rise of 0.4–0.7°C, a significant difference (p<0.001) from those given normal saline. However, the difference in Tr between the animals given MKK or GKT and those given normal saline was not significant in the statistical assay. Importantly, significant differences with p values of 0.001 less were found between Eph and MKK and between Eph and GKT (Fig. 5).

Relaxant Effects on Tracheal Smooth Muscle (in Vitro)
The relaxant effects of Eph and MKK were evaluated with Magnus’s method in vitro (Fig. 6). The result indicated that the potency of MKK at a final concentration of $1.3 \times 10^{-4}$ g/ml was similar to that of Eph at a final concentration of

![Diagrams showing changes in CEWL, CDHL, RDHL, and Tr with dose (mg/kg) for Eph, MKK, and GKT.](image)

**Table 1.** Details of Traditional Medicines

<table>
<thead>
<tr>
<th>Material</th>
<th>Daily dose/Ephedrine content (mg)</th>
<th>Experimental dose (mg/kg)</th>
<th>Content of main component (mg/Expl. dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ephedrine</td>
</tr>
<tr>
<td>MKK</td>
<td>2250/35.37</td>
<td>127.22</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>254.45</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>508.90</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>164.06</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>328.12</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>656.24</td>
<td>8.00</td>
</tr>
<tr>
<td>GKT</td>
<td>2100/25.60</td>
<td>200.00</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400.00</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800.00</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1600.00</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3200.00</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6400.00</td>
<td>8.00</td>
</tr>
</tbody>
</table>

The methods of the quantitative analysis by HPLC were given in the previous paper.\textsuperscript{15}
1.0×10^{-6} g/ml. The relaxation of MKK mainly depended on its Eph content (Table 1).

DISCUSSION

The main crude drug in MKK and GKT is ephedra herb of which the effective component is ephedrine. GKT is the combination of an additional mulberry bark to MKK. Both medicines are used to treat upper respiratory diseases, such as hot-type asthma with thirst and sticky sputum, while "Sho-seiryu-to (小青竜湯, SST)" is used for cold-type asthma with watery sputum. A distinction between Hot-syndrome and Cold-syndrome is drawn in traditional medicine for their applications. In modern medicine, bronchial asthma is also classified into dry cough and wet cough, which classification is closely correlated with Cold-hot syndrome in traditional medicine. If in addition to asthmatic symptoms, Cold-hot syndrome is an important criterion for the use of SST, MKK or GKT in treatment of asthma, the adaptation syndrome of these medicines must be experimentally evaluated. The device to measure insensible perspiration and body temperature was therefore developed to determine their effects, and the results have been of great interest, as reported. In this study, MKK and GKT used in the treatment of hot-type asthma were tested in detail.

MKK showed a similar relaxation of tracheal smooth muscle to that of ephedrine in the in vitro experiments (Fig. 6), by which its antagonistic effect was assessed. The experimental data also suggested that its effects and potency were dependent upon Eph without the interference of other components. Further, although Tr of the animals given Eph markedly increased, MKK or GKT containing the same amount of Eph did not increase Tr and there was no statistically significant difference in comparison to the saline control. It was obvious that this effect must be due to the components in the additional comprised crude drugs. In other words, MKK or GKT preserved the relaxant effects of ephedrine on tracheal smooth muscle, but prevented it from raising Tr. The result was also explained by the fact that CDHL was markedly reduced in the administration of MKK or GKT. Therefore, if a predisposition to hyperthermia or fever is a fundamental disease factor for sufferers from hot-type asthma or dry cough, the administration of Eph or theophylline is physiologically undesirable. Consequently, the syndrome of MKK or GKT was experimentally determined. Their preventive mechanism against the rise in Tr was not associated with non-evaporative heat loss, because the administration of MKK or GKT not only exhibited similar RDHL to that of normal saline control, but also lowered CDHL. Since both effects on REWL were similar to that of Eph, insensible perspiration also did not take part in the mechanism of preventing the rise in Tr. This evidence suggested that the antagonistic effect of both prescriptions on Tr may be involved in heat production, rather than non-evaporative heat loss or insensible perspiration, as shown diagrammatically Fig. 7. In any event, Eph or MKK or GKT all increased REWL. However, the markedly increased action of Eph on REWL was the response to the rise in Tr, which was explained by a slight increase in RDHL and similar CDHL and CEWL to that of control trials. The increase in REWL by MKK or GKT that followed the reduction in CDHL was based on normal Tr, which was essentially different from Eph. Moreover, with the maintenance of normal Tr and local temperature of respiratory organs, the action of both medications could keep the drying respiratory tract at a higher humidity. The results predict that sputum at a lower viscosity could be easily coughed up. Our experimental evidence may explain traditional Chinese medical theory for the clinical uses of MKK and GKT.

The distribution of syndromes in adult patients suf-
ferring from bronchial asthma is illustrated in Fig. 8 according to clinical observations made by Egashira. Additionally, the children cases are mostly hot-type asthma. In modern therapy, Eph or theophylline agents or similar drugs are clinically employed for most of these cases. When they demonstrate a poor effect for a heavy attack, steroid treatments are carried out. In none of these treatments has the syndrome type (cold-type or hot-type) that is the criterion for medicine application in traditional medical therapy been taken into consideration. However, our experimental data indicated that Eph and theophylline acted to raise Tr. From the point of view of traditional medical theory, they may be attributed to the antiasthmatics of heating or warming property. Thus, their application for patients in group B in Fig. 8., i.e., the cold-type patients, should be effective and desirable. For the patients in group A in Fig. 8, however, even if they can reduce the asthmatic symptoms due to the relaxant action on bronchial smooth muscle, their increased action on Tr may have a physiologically negative impact on the function of the body. If the symptoms of hot-type sufferers from asthma are based on the loss of body fluid due to fever, these drugs are not undesirable. The in vitro experiments proved that MKK did have a relaxant action on the smooth muscle. Depending on its Eph contents, it is assumed that GKT should show a similar relaxant activity. If the action is due to Eph, it suggests that both medicines have the antiasthmatic action with an insight into symptomatic therapy. That is to say, both shared the bronchodilation of Eph, but the action of the ephedra herb on Tr was prevented by the composition of other crude drugs. As a consequence, both MKK and GKT are adaptable to patients in group A (hot-type patients). In fact, their application is targeted at bronchial asthma with hot-syndrome such as manifested by thirst, stick sputum, an excessive sweating and fever in traditional medical treatment. Our data experimentally supports the clinical report that MKK and GKT are effective for youth or children suffering from asthma and can relieve the asthmatic attacks of children. In addition, it is interesting to note that their action of increasing REWL not only benefits the drying conditions of airway, but also kept the dry cough cases in a desirable condition.

The antagonistic effects of MKK or GKT against the ephedra herb are probably linked to gypsum, a cooling agent with the action of heat-clearing, as well as to the action of apricot kernel and glycyrrhizin. The elucidation of their interaction is now in progress.

In conclusion, our experiments indicate that it is undesirable to use Eph or theophylline to treat asthma which is accompanied by such symptoms as thirst, fever or sticky sputum because of the increased actions of both drugs on Tr. MKK and GKT, on the contrary, both of which are ephedra herb combinations, are adaptable for the hot-type asthma because they prevent a rise in Tr. Thus, the treatment of asthma requires a better understanding of such medicinal properties as cooling, heating or warming actions. MKK and GKT are particularly advantageous for the treatment of bronchial asthma, because there are few modern drugs with the cooling action adaptable to hot-type asthma. Nevertheless, it should be pointed out that side effects or the aggravation of disease may be elicited regardless of the actions of antiasthmatics on constitutional predispositions such as Tr, body fluid, and so on.

Acknowledgments This study was supported by research funds from “The Traditional Oriental Medical Science Program” of the Public Health Bureau of Tokyo Metropolitan Government. The authors also would like to thank Asahi Beer Pharmaceutical Co., Ltd. and Kanebo Pharmaceutical Co., Ltd. for their supply of samples.

REFERENCES

3) “Chugoku Kampo Igaku Gairon (中国漢方医学概論),” ed. by Nanjing College of Chinese Traditional Medicine (Translated by Chuigakugaku shiyou (nihon yōkuan)), Chugokumoku, Tokyo, 1974, pp. 46—53.