against an oral infection with *Listeria monocytogenes*. *Immunopharmacol.*, **39**, 215-223.

33. ZHU, Z., TANG, W., RAY, A., WU, Y., EINARSSON, O., LANDRY, M.L., GWALTNEY, J, JR. & ELIAS, J.A. (1996). Rhinovirus stimulation of interleukin-6 in vivo and in vitro. Evidence for nuclear factor kappa B-dependent transcriptional activation. *J. Clin. Invest.*, **97**, 421-430.

Figure legends

Figure 1. (a) The time course of viral release in supernatants of human tracheal epithelial cells obtained at different times after exposure to 10^5 $TCID_{50}$ units per ml of RV14 in the presence of hochu-ekki-to (100 ng/ml) (closed circles) or vehicle of hochu-ekki-to (DMSO, 0.2 %) (open circles). The rates of change in RV14 concentration in the supernatant are expressed as $TCID_{50}$ units/ml/24h. Results are means ± s.e. from 5 different tracheae. Significant differences from viral infection alone are indicated by $*P<0.05$ and $**P<0.01$.

(b) Time course of replication of rhinovirus RNA from human tracheal epithelial cells after infections of RV14 in the presence of hochu-ekki-to (100 ng/ml; closed columns) or DMSO (0.2 %) as a vehicle of hochu-ekki-to (control; open columns) as detected by real-time quantitative amounts of RT-PCR. Results are expressed as relative amounts of RNA expression (%) compared with those of maximal RV14 RNA at day 5 (120 h), and reported as means + s.e. from 5 samples. Significant differences from treatment with a vehicle of hochu-ekki-to (control) at each time are indicated by $*P<0.05$ and $**P<0.01$. To examine the effects of hochu-ekki-to on viral RNA in the cells, the cells were treated with hochu-ekki-to (100 ng/ml) or a vehicle of hochu-ekki-to from 3 days before RV14 infection to the RNA extraction after RV14 infection. The RNA extraction was performed at either 0, 24, 72 or 120 h after RV14 infection.

Figure 2. Concentration-response effects of hochu-ekki-to (a), glycyrrhizin (b) and hesperidin (c) on the viral release in supernatants collected during 24 h to 72 h after infection. The cells were treated with hochu-ekki-to, glycyrrhizin,

hesperidin or vehicle (Control; DMSO, 0.2 %, open circles) from 3 days before RV14 infection until the end of the experiments after RV14 infection. The rates of change in RV14 concentration in the supernatant are expressed as $TCID_{50}$ units per/ml/24h. Because hochu-ekki-to is a mixture of various herbs, the concentration of hesperidin has been used as an indicator of the concentration of hochu-ekki-to in supernatant. However, in this figure, the concentration of glycyrrhizin was used as an indicator of the concentration of hochu-ekki-to in supernatant in order to compare the inhibitory effects of hochu-ekki-to with those of glycyrrhizin. Analysis of the biochemical composition of hochu-ekki-to with 3D HPLC suggests that hochu-ekkito (1g) contains the same level of hesperidin (5.7 mg) and glycyrrhizin (5.0 mg) (data from Tsumura Co.). Results are means ± s.e. from 5 different tracheae. Significant differences from vehicle alone (control) are indicated by $*P<0.05$ and $**P<0.01$.

Figure 3. (a) The expression of ICAM-1 mRNA in human tracheal epithelial cells 3 days after treatment with hochu-ekki-to (Hochu-ekki-to, 100 ng/ml, closed column) or vehicle of hochu-ekki-to (0.2 % DMSO, control, open column) detected by real-time quantitative RT-PCR. ICAM-1 mRNA was normalized to the constitutive expression of GAPDH mRNA. Results are means + s.e. from 5 different tracheae. Significant differences from control values are indicated by $**P<0.01$.

(b) The sICAM-1 concentrations in supernatants of human tracheal epithelial cells 3 days after treatment with hochu-ekki-to (Hochu-ekki-to, 100 ng/ml, closed column) or vehicle of hochu-ekki-to (0.2 % DMSO, control, open column). In order to examine the effects of hochu-ekki-to on sICAM-1 concentrations in supernatants, the cells were treated with hochu-ekki-to or

vehicle for 3 days before RV14 infection. At 1 day before RV14 infection, cells were rinsed with PBS and fresh DF-12 medium containing 2% USG was replaced. Then, supernatants were collected just before RV14 infection and the sICAM-1 concentrations in supernatants were measured. Results are means + s.e. from 5 different tracheae. Significant differences from control values are indicated by $**P<0.01$.

Figure 4. Time course of release of cytokines into supernatants of human tracheal epithelial cells after infection of RV14 in the presence of hochu-ekki-to (100 ng/ml) or vehicle of hochu-ekki-to (DMSO, 0.2%), or after UV-inactivated RV14 (UV-RV14). The rates of change in cytokines concentration in the supernatant are expressed as pg/ml/24h. Results are means + s.e. from 5 different tracheae. Significant differences from values before RV14 infection (time 0) in the presence of vehicle of hochu-ekki-to (DMSO, 0.2%) are indicated by $*P<0.05$ and $**P<0.01$. Significant differences from corresponding values of RV14 alone (RV14) are indicated by $+P<0.05$.

Figure 5 (a) Changes in the distribution of acidic endosomes with green fluorescence in the human tracheal epithelial cells before (time 0 sec) and 300 sec (time 300 sec) after treatment with hochu-ekki-to (Hochu-ekki-to, 100 ng/ml). Data are representative of 3 different experiments.

(b) Time course changes in the intensity of green fluorescence from acidic endosomes in human tracheal epithelial cells after treatment with either hochu-ekki-to (100 ng/ml, closed circles) or vehicle of hochu-ekki-to (0.2 % DMSO, open circles). Inhibitors were administrated at time 0.

(c) The fluorescence intensity of acidic endosomes 300 sec after the addition of hochu-ekki-to (Hochu-ekki-to 100 ng/ml, closed column) or vehicle of

hochu-ekki-to (0.2 % DMSO, Control, open column). Results are means + s.e. from 5 different tracheae. Significant differences from control values are indicated by *P<0.05.

Subjects who received antiemetics at the time of administration had better tolerance of tigecycline. Older patients and men also reported less nausea than younger subjects and women.[7]

Related to clinical indications, tigecycline has been approved for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections, although in Argentina, in the first month after launch, 61% of the tigecycline prescriptions were "off label," especially in older patients with VAP due to MDR *Acinetobacter* spp. (unpublished data). The high concentration in alveolar cells (77.5 times as high as in serum),[6] the increase of carbapenem-resistant *Acinetobacter* spp. in Argentina (54%),[8] and the association between the initial inappropriate antibiotic therapy with mortality in patients with VAP[9] seem to be the main reasons for using tigecycline in this indication.

We believe that tigecycline presents several beneficial features for treating critically ill older patients with VAP (Table 1): an antibacterial spectrum that includes multiresistant bacteria, the lack of a need for adjustment of dosage to renal function, the low probability of drug interactions, and mild to moderate side effects.

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REFERENCES

1. Turnheim K. Drug dosage in the elderly. Is it rational? Drugs Aging 1998;13:357–379.
2. Wyeth Pharmaceutics. Tygacil (Tigecycline) for Injection [Package Insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., 2005.
3. de Mendonca A, Vincent JL, Suter PM et al. Acute renal failure in the ICU. Risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000;26:915–921.
4. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. Clin Infect Dis 2006;43(Suppl 2):S89–S94.
5. Troy SM, Muralidharan G, Micalizzi M et al. The effects of renal disease on the pharmacokinetics of tigecycline (GAR-936) [abstract A-43]. In: Program and Abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, 2003, p 5.
6. Pankey GA. Tigecycline. J Antimicrob Chemother 2005;56:470–480.
7. Stein GE, Craig WA. Tigecycline: A critical analysis. Clin Infect Dis 2006; 43:518–524.
8. Pasterán F, Rapoport M, Petroni A et al. Emergence of PER-2 and VEB-1a in Acinetobacter baumannii strains in the Americas. Antimicrob Agents Chemother 2006;50:3222–3224.
9. Luna C, Aruj P, Niederman M et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. Eur Respir J 2006;27:158–164.

THE TRADITIONAL HERBAL MEDICINE HOCHUEKKITO IMPROVES SYSTEMIC INFLAMMATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the Editor: Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability throughout the world. The risk of airflow limitation is significantly greater with older age.[1] The chronic pulmonary inflammatory process in patients with COPD has systemic repercussions. The effect of the systemic manifestations of COPD on the prediction of mortality using a multidimensional index has recently been reported.[2] We investigated the effects of the traditional herbal medicine Hochuekkito (Bu-Zhong-Yi-Qi-Tang) on systemic inflammation in older patients with COPD whose forced expiratory volume in 1 second (FEV_1)/forced vital capacity was less than 70%. One randomized, controlled trial of Hochuekkito showed that the quality of life and immunological status of elderly patients improved during treatment.[3]

Thirty-five consecutive and clinically stable patients with COPD (mean age ± standard error 73 ± 1) were prospectively and randomly divided into two groups. One group (n = 17) was given 7.5 g of Hochuekkito extract daily in addition to inhaled bronchodilators, whereas the control group (n = 18) continued to use previously prescribed bronchodilators. The daily dose of Hochuekkito extract was divided into three doses of 2.5 g each to be taken orally 30 minutes before each meal for 6 months. A controller determined whether Hochuekkito was given to patients. There were no significant differences between the two groups regarding age, sex, body mass index (19.3 ± 0.7 vs 20.7 ± 0.8 kg/m^2), or the results of pulmonary function tests (FEV_1%predicted 40.7 ± 5.0% vs 45.4 ± 2.3%).

Serum inflammatory markers were examined before and after the treatment period. Previous studies have demonstrated that serum C-reactive protein (CRP) is higher in patients with COPD without clinically relevant ischemic heart disease independent of smoking, whereas it is lower in patients with COPD receiving inhaled corticosteroid therapy.[4–6] Serum CRP correlated negatively with FEV_1%predicted, a marker of COPD severity, before treatment ($r = -0.43$, $P < .001$). Serum CRP did not differ significantly between the two groups before treatment ($P = .08$). In the Hochuekkito-treated group, serum CRP decreased significantly, from 3,230 ± 450 to 2,060 ± 330 ng/mL ($P < .01$), whereas it was unchanged in the control group (Figure 1).

Regarding markers of systemic inflammation in COPD, serum tumor necrosis factor alpha (TNF-α; $r = -0.42$, $P < .001$) and interleukin (IL)-6 ($r = -0.21$, $P < .001$) also correlated negatively with FEV_1% predicted at baseline. The pretreatment value of serum TNF-α was significantly higher ($P = .02$) in the Hochuekkito-treated group and decreased significantly from 3.6 ± 0.6 pg/mL to 2.1 ± 0.4

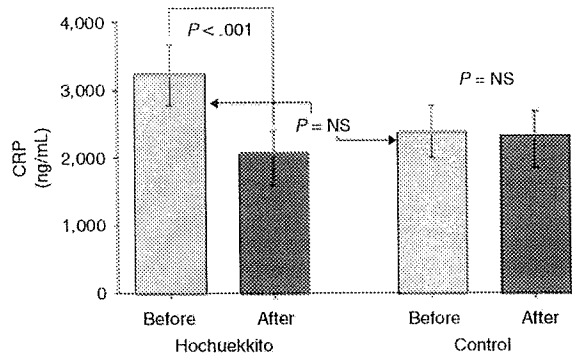

Figure 1. Serum C-reactive protein (CRP) values before and at the end of the study period. Serum CRP did not differ significantly between the two groups before treatment ($P = .08$). In the Hochuekkito-treated group, the mean value ± standard error of serum CRP decreased significantly from 3,230 ± 450 ng/mL to 2,060 ± 330 ng/mL ($P < .01$). In the control group, serum CRP remained unchanged from 2,380 ± 380 ng/mL to 2,380 ± 360 ng/mL during the study period. NS = not significant.

pg/mL after treatment, whereas it was unchanged in the control group (2.2 ± 0.3 pg/mL before and after treatment). Serum IL-6 remained unchanged in both groups. In the Hochuekkito-treated group, serum prealbumin level, a marker of nutritional status, increased from 23.6 ± 1.1 mg/dL to 26.6 ± 1.2 mg/dL, whereas it was unchanged in the control group.

These data suggest that Hochuekkito improves systemic inflammation and nutritional status in older patients with moderate to severe COPD, although the mechanisms of Hochuekkito have not been defined. Systemic inflammation, in addition to nutritional status, is a determinant of quality of life and prognosis in COPD patients.[2,7] Further larger studies on its effects and mechanisms of action will be needed, although Hochuekkito has a long history of use in patients with COPD and weakness, and its safety has been clinically established.

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REFERENCES

1. Tatsumi K, Sakao S, Igari H et al. Clinical phenotypes of chronic obstructive pulmonary disease: Results of a nationwide epidemiological survey in Japan. Respirology 2004;9:331–336.
2. Celli BR, Cote CG, Marin JM et al. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–1012.
3. Satoh N, Sakai S, Kogure T et al. A randomized double blind placebo-controlled clinical trial of Hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness N of one and responder restricted design. Phytomedicine 2005;12:549–554.
4. Pinto-Plata VM, Müllerova H, Toso JF et al. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax 2006;61:23–28.
5. de Torres JP, Cordoba-Lanus E, Lopez-Aguilar C et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. Eur Respir J 2006;27:902–907.
6. Sin DD, Lacy P, York E et al. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:760–765.
7. Schols AM, Slangen J, Volovics L et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1791–1797.

SIMPLE COGNITIVE TESTING (MINI-COG) PREDICTS IN-HOSPITAL DELIRIUM IN THE ELDERLY

To the Editor: Cognitive impairment is a well-known risk factor for delirium.[1–4] Delirium, in turn, is also a marker of risk for the development of dementia, even in older individuals without prior cognitive or functional impairment.[5] Obtaining a cognitive assessment on patients admitted acutely to the hospital is challenging. A simple cognitive test that a range of healthcare professionals could easily administer would facilitate assessment of people at risk for delirium. The Mini-Cog is a simple tool to screen for cognition that has been validated in a population-based sample of ethnically and linguistically diverse older adults. It takes 3 minutes to administer, performs as well as or better than the Mini-Mental State Examination for screening for dementia, and is not influenced by language and education.[6–9] This study aimed to evaluate the usefulness of the Mini-Cog, a simple cognitive test as a predictor of in-hospital (incident) delirium in older people.

STUDY DESIGN

This is a prospective cohort study. The study population consisted of patients aged 65 and older admitted consecutively to general medical teaching units at the University of Alberta Hospital in Edmonton over a period of 7 months. After obtaining informed consent (from the patient or proxy), all patients who were willing to participate and who were deemed to be at high risk for delirium were included in the study. Patients were screened for high risk using a delirium risk questionnaire, which was based on information from the literature. High risk was defined as cognitive impairment, aged 80 or older, or any two of the following comorbidities: functional impairment, special sensory impairments (hearing or vision impairment), or critical