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It has been reported that vitamin K analogues have various pharmacological effects such as antiviral, antifungal, anticancer, and antiplatelet activities. It has also been reported that some synthetic naphthoquinone compounds showed antiplatelet activities. In the present study, the antithrombotic activity of VK-708 (2-[N-2-bromo-4-fluoro-phenyl]amino-3-chloro-5-hydroxy-1,4-naphthoquinone), a newly synthesized vitamin K derivative, was investigated. Effects of VK-708 on the murine pulmonary thrombosis *in vivo*, human platelet aggregation *in vitro*, rat platelet aggregation *ex vivo*, and coagulation parameters were examined. VK-708 prevented the death due to pulmonary thrombosis in mice dose-dependently *in vivo*. It also inhibited ADP- and collagen-induced rat platelet aggregation *ex vivo* in a dose-dependent manner. Moreover, VK-708 potently inhibited collagen-, thrombin-, and A23187-induced aggregation in washed human platelet concentration dependently *in vitro*. VK-708, however, did not alter such coagulation parameters as activated partial thromboplastin time and prothrombin time in human plasma.
These results suggest that VK-708 may be a promising antithrombotic agent, and the antithrombotic activity of VK-708 may be due to the antiplatelet activity, but not to anticoagulation activity.

[PA1-15] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Effects of nalbuphine on the development of morphine-induced tolerance and dependence in rats

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Morphine is central to the treatment of many types of chronic pain. But the development of tolerance to morphine can become a problem, most notably in pain therapy in opioid addicts. The purpose of the present study was to investigate whether combined administration with nalbuphine affect development of tolerance and dependence to continuous exposure to morphine. Morphine (10 mg/kg) was injected intraperitoneally for 5 days. Nalbuphine (0.1, 1.0 and 5.0 mg/kg) was administered IP in combination with morphine injection. Morphine tolerance was assessed antinociceptive effect by the Randall-Selitto test. Morphine dependence was determined by precipitated withdrawal signs induced by naloxone (10 mg/kg, IP). Nalbuphine did not attenuate morphine-induced antinociceptive effect in rats. Combined administration of nalbuphine with morphine significantly inhibited the development of morphine tolerance and dependence We hypothesize that the use of compounds such as nalbuphine may prove to be useful adjunct therapy in the management of some forms of clinical pain by morphine.

[PA1-16] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Nonpeptide Angiotensin II Receptor Antagonist, Studies with BR-A-657

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BR-A-657(2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3- [[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl] pyrimidin-4(3H)-one, potassium salt·$3H_2O$) is shown to be a novel, nonpeptide, antihypertensive, specific angiotensin II (AII) receptor antagonist. In rabbit aorta, it noncompetitively inhibited the contractile response to AII with pD_2 9.05. In guinea pig ileum, it inhibited the responses to AI and AII (IC_{50} 0.89 and 0.5 nM, respectively). In conscious normotensive rats, BR-A-657 (0.01, 0.1, 1 mg/kg i.v.) inhibited AII-induced pressor responses in a dose-dependent manner (ID_{50} 0.02) and BR-A-657 (0.3, 1, 3 mg/kg p.o.) produced long lasting inhibition of AII pressor responses (ID_{50} 0.32). In renal