The reason for the retarded elimination is not apparent from our data.

Conclusion. Our results show that in fact ethanol can affect the conjugation of isoniazid in vivo. As mice oxidize ethanol much faster than men[13], our data may be valid only for this species and the high dose of ethanol that had to be applied, but considering the different toxicity and therapeutic efficacy of free and conjugated isoniazid, and the fact that pharmacodynamic interactions have been reported[12], it appears to be worthwhile to search for pharmacokinetic interactions of ethanol and isoniazid also in humans. The results obtained with the sulfonamides, being less clear-cut, are not indicative of a significant interaction of these drugs and ethanol.

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Pharmacological studies of a new analgesic, dl-erythro-1-phenyl-2-(o-chlorophenyl)-2-[4-(p-methoxybenzyl)-1-piperazinyl] ethanol dihydrochloride, in experimental animals

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Summary. dl-Erythro-1-phenyl-2-(o-chlorophenyl)-2-[4-(p-methoxybenzyl)-1-piperazinyl] ethanol dihydrochloride showed orally a definite analgesic activity, without producing the significant morphine-like physical dependence liability, and its analgesic potency was about a half that of codeine and far superior to aminopyrine in experimental animals.

Analgesic activity of derivatives of 1,2-diphenyl-2-piperazinyl-ethanol has been tested in experimental animals. Subsequently, it was found that dl-erythro-1-phenyl-2-(o-chlorophenyl)-2-[4-(p-methoxybenzyl)-1-piperazinyl] ethanol dihydrochloride (DU-608, figure 1) possessed a comparatively potent analgesic activity by oral application without producing the significant morphine-like physical dependence liability.

Methods and results. I.v. analgesic activity of DU-608, codeine phosphate(codeine) and d-propoxyphene hydrochloride (d-propoxyphene), by the method of mechanical pressure stimuli[1,2], is shown in figure 2. Analgesic ED50-values (mg/kg) and 95% confidence limits of DU-608 in rats and mice were 2.94 (2.00–4.40, n = 40) and 4.04 (2.99–5.46, n = 51), respectively, and its activity was approximately comparable to that of d-propoxyphene and codeine, and far superior to that (ED50 = 73.0, n = 30 in mice) of aminopyrine. As shown in figure 3, DU-608, administered orally, produced a dose-dependent inhibition of the pain-like response induced by stimulating electrically a tooth pulp through the electrodes implanted chronically in conscious dogs[3,4]. The potency of DU-608 (ED50 = 50.1 mg/kg) was about a half that of codeine (28.1 mg/kg) and superior to that of aminopyrine (almost inactive). The oral activity of DU-608 to abolish the pain-like responses induced by various nociceptive stimuli (chemical[5], mechanical pressure[1,2], radiant heat[1,6]) in mice and rats was superior to that of pentazocine and aminopyrine, and a half or one-third that of codeine and d-propoxyphene. Its therapeutic index (LD50/ED50) was higher than that of pentazocine and aminopyrine, and higher than or at least equal to that of d-propoxyphene.

Anti-writhing (phenylquinone induction) activity of DU-608 was antagonized by naloxone hydrochloride similar to that of pentazocine, codeine and d-propoxyphene in mice. On the other hand, analgesic activity (by the radiant heat method) of 5 mg/kg, s.c., of morphine hydrochloride(morphine) was only slightly enhanced by the simultaneous administration of 160 mg/kg, s.c., of DU-608 (ED50 = 80 mg/kg, s.c.), but not affected by the administration of 20 to 80 mg/kg in mice. Furthermore, Straub tail elevating activity of morphine (10 mg/kg, i.v.) was neither additively enhanced nor antagonized by a s.c. administration of up to 160 mg/kg of DU-608. The activities of morphine were enhanced or antagonized by the simultaneous administration of codeine or pentazocine, respectively.

No significant withdrawal syndrome was observed by an abrupt withdrawal of DU-608 or by an administration of levallorphan tartrate (10 mg/kg, s.c.) instead of DU-608 in the rats, receiving the chronic administration of DU-608 (the maximal daily tolerant dose; 48 mg/kg, s.c., or 400 mg/kg, p.o.) twice daily for 7–8 weeks. The rats, receiving chronically codeine (60 mg/kg/day, s.c., or 80 mg/kg day,

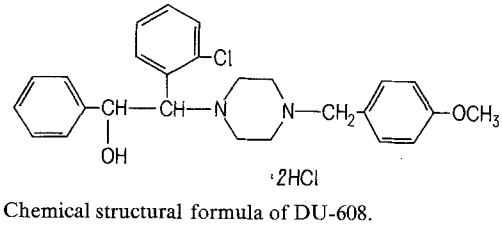

Fig. 1. Chemical structural formula of DU-608.

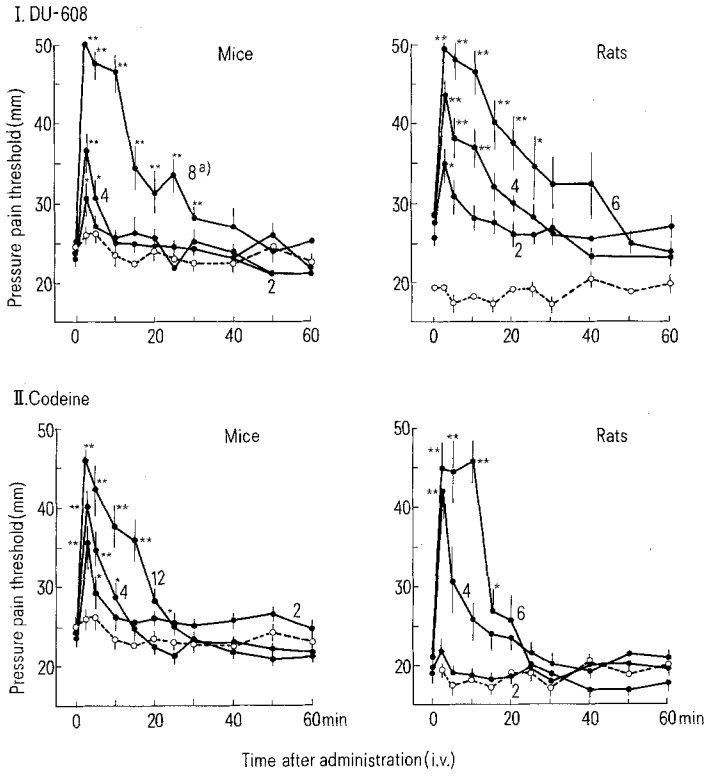

Fig. 2. I.v. analgesic activity of DU-608 and codeine in mice and rats. Mechanical pressure pain was induced by pressing the tail of male mice of STDddY strain or male rats of Wistar strain using an apparatus which consists of a fixed plate and a movable rod with a sharp tip (1 mm wide and 5 mm long). The pressure pain threshold, the biting response, was measured after drug administration in mm (1 mm = 12.5 g pressure) with an arbitrary cutoff pressure of 50 mm. Each point and vertical bar represent the mean and SEM from more than 10 animals. $*0.01 < p < 0.05$; $**p < 0.01$, significantly different from each value of time 0. [a]Dose in mg/kg, i.v. ○: Vehicle group.

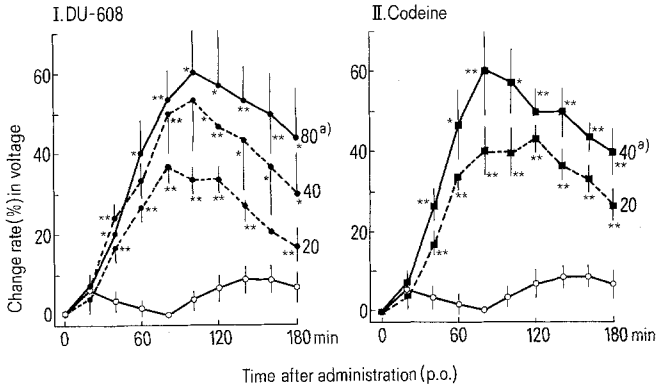

Fig. 3. Effect of DU-608 and codeine on the pain-like response induced by electrical stimulation of a tooth pulp in conscious dogs. 2 platinum electrodes were inserted in a left canine of mongrel dogs (8–12 kg). 1 week or more after the operation, the tooth pulp of each dog was stimulated with a frequency of 30 Hz and a duration of 5 msec for 3 sec at the intervals of 20 min without anaesthesia. The intensity of each successive stimulus was increased by 10% of the preceding value until the pain threshold response was observed. Drugs were orally administered as a suspension or a solution in 0.5% gum tragacanth aqueous solution. The threshold voltage of normal dogs was 3–10 volts. Each point and vertical bar represent the mean percent increase and SEM from 3 dogs in the threshold voltage from time 0. $*0.01 < p < 0.05$; $**p < 0.01$, significantly different from each vehicle control group (open circle). [a]Dose in mg/kg, p.o.

p.o.), exhibited the marked and definite withdrawal syndromes on an abrupt withdrawal of codeine or the levallorphan administration. When the morphine-dependent rats, receiving chronically morphine twice daily for more than 7 weeks (the maintenance dose of 200 mg/kg/day, s.c.), were given s.c. 100–400 mg/kg day of DU-608 instead of morphine for 1 day, the rats showed the marked withdrawal syndromes similar to those seen in the rats given saline.

Discussion. DU-608 showed the definite inhibitory activity on the pain-like responses induced by various nociceptive stimuli in mice, rats and dogs, and its anti-writhing activity was antagonized by naloxone like codeine and pentazocine. However, DU-608 neither enhanced additively the analgesic activity and Straub tail reaction of morphine, nor showed the significant morphine-like physical dependence liability in rats.

DU-608 is the racemate, and the analgesic activity of the R-isomer, (d)-erythro-1(S)-phenyl-2(R)-(o-chlorophenyl)-2(R)-[4-(p-methoxybenzyl)-1-piperazinyl] ethanol dihydrochloride, is about 4 times potent that of the S-isomer[7]. Namely, the C-2 position of the R-isomer shows the reverse configuration to morphine(C-9) and (l)-1, 2-diphenyl-1-dimethylaminoethane(lefetamine), an analgesic, which has a stereochemical resemblance to morphine[8]. Accordingly, the pharmacological properties described above of DU-608 may be attributable to a stereochemical difference between DU-608 and morphine.

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