REFERENCES

Baskin, S. I. Dagirmanjian, R. (1973) Nature (London) 245: 464–465

Bianchi, C. P. (1962) J. Pharmacol. Exp. Ther. 138: 41

Chan-Palay, V., Engel, A. G., Jang-Yen, W., Palay, S. L. (1982) Proc. Natl. Acad. Sci. 79: 7027–7030

Chovan, J. P., Kalakowski, E. C., Sheakowski, S., Schaffer, S. W. (1980) Mol. Pharmacol. 17: 295–300

Duncan, C. J., Smith, J. L. (1978) Naunyn-Schmiedeberg's Arch. Pharmacol. 305: 159–166

Durelli, L. Mutani, R. (1979) J. Neurol. Sci. 42: 103–109

Endo, M. (1977) Physiol. Rev. 57: 71–108

Franconi, F., Stendardi, I., Martini, F., Zilletti, L., Giotti, A. (1982a) J. Pharm. Pharmacol. 34: 329–330

Franconi, F., Giotti, A., Manzini, S., Martini, F., Stendardi, I., Zilletti, L. (1982b) Br. J. Pharmacol. 75: 605–612

Gruener, R., Markowitz, D., Huxtable, R., Bressler, R. (1975) J. Neurol. Sci. 24: 351–360

Hilton, J. G. (1977) J. Pharmacol. Exp. Ther. 203: 426–434

Huxtable, R., Bressler, R. (1973) Biochim. Biophys. Acta 323: 573–583

Jacobsen, J. G., Smith, L. H. (1968) Physiol. Rev. 48: 424–511

Muramatsu, M., Kakita, H., Nakagawa, K., Kuriyama, K. (1978) Jpn. J. Pharmacol. 28: 259–268

Raghu, C. N., Manikeri, S. R., Dadkar, V. N., Streth, U. K. (1980) Ind. J. Exp. Biol. 18: 1468–1470

Read, W. O., Jaqua, M. J., Steffen, R. P. (1980) Proc. Soc. Exp. Biol. Med. 164: 576–582

Weber, A., Herz, R. (1968) J. Gen. Physiol. 52: 750–759

Wilson, B. W., Peterson, D. W., Lilyblade, N. L. (1965) Proc. Soc. Exp. Biol. Med. 119: 104–108

J. Pharm. Pharmacol. 1984, 36: 61–63
Communicated May 12, 1983

Increased brain uptake of morphine in the presence of the antihistamine tripelennamine

N. L. VADLAMANI, R. B. PONTANI, A. L. MISRA*, *New York State Division of Substance Abuse, Research Laboratory, 80 Hanson Place, Brooklyn, N.Y. 11217, and State University of New York, Department of Psychiatry, Downstate Medical Center, Brooklyn, N.Y. 11203, U.S.A.*

Disposition of [6 ^{3}H (N)]morphine in plasma, brain and liver of rats was studied 15 min after intravenous injection of either a 2 mg kg^{-1} dose of morphine or a combination of the same dose of morphine with a 6 mg kg^{-1} dose of tripelennamine. The concentrations of morphine in brain and the brain to plasma morphine ratios in animals receiving the combination of drugs concurrently were significantly higher than those in the control morphine group. No significant differences were seen in the morphine or morphine metabolite concentrations in plasma and liver or liver to plasma morphine concentration ratios in the 2 groups. Data suggest that pharmacokinetic factors play a role in the potentiation of opiate effects by antihistamine on concurrent i.v. administration of the two drugs.

Intravenous abuse of combinations of the antihistamine tripelennamine (Pyribenzamine) with pentazocine (Bhargava 1981; Poklis 1982) or paregoric and morphine (Wendt et al 1964; Burton et al 1965; Szwed 1970) recognized under the street names of 'T's and Blues' and 'Blue Velvet' respectively among heroin addicts in major metropolitan areas of midwestern U.S.A., have received increasing attention in the last five years. These combinations reportedly produce a heroin-like 'rush' sensation lasting for 5 to 10 min, followed by a feeling of well-being over the next 4 h. The addicts carefully establish a correct ratio for these drugs by titrating themselves to get the sought-after 'high', while avoiding a seizure. The abuse of such combinations is potentially dangerous and sometimes fatal. A non-lethal dose of tripelennamine in combination with pentazocine resulted in a significant decrease in the LD50 of pentazocine from 116 to 60 mg kg^{-1} i.p. in mice (Waller et al 1980). Concomitant s.c. administration of tripelennamine with pentazocine or morphine shifted the dose-response curve of the opiate to the left and enhanced the duration of the antinociceptive effect of narcotics (Tagashira et al 1982) and morphine-like discriminative stimulus effects of pentazocine (Shannon & Su 1982). At present, the rationale underlying the use of combinations of an antihistamine and opiate and the enhancement of narcotic effects is not clear. This investigation was undertaken to determine any possible role of altered distribution factors in the potentiation of opiate effects on concurrent i.v. administration of tripelennamine and morphine.

* Correspondence.

Methods

Samples of drugs. Tripelennamine hydrochloride was a gift from Ciba-Geigy Corp., Summit, N.J [6-^{3}H (N)]-morphine, specific activity 9·84 Ci m mol^{-1} was obtained commercially from New England Nuclear Corp. Boston, Mass. The ethanol solution of the

labelled drug was transferred to a volumetric flask and the solvent evaporated under a stream of nitrogen. The residue was taken up in required amount of 0·001 M hydrochloric acid and suitably diluted with non-labelled morphine hydrochloride in 0·9% NaCl (saline) to furnish the injection solution (2 mg ml^{-1}, sp. activity of drug 10 μCi mg^{-1}). The injection solution of drugs in combination contained 2 and 6 mg ml^{-1} of morphine and tripelennamine respectively in saline. All concentrations are expressed as free base. The pH of morphine injection solution was 5·65, and that of drugs in combination 6·25.

Estimation of [^{3}H]morphine in biological materials. Aliquots (2 ml) of plasma (diluted 1 : 5 with distilled water) or tissue homogenates (10% w/v in 0·5 M HCl) containing 1 ml of non-radioactive morphine hydrochloride as carrier (500 μg ml^{-1} as free base) were adjusted to pH 9–9·5 with 1 M NaOH and the solution was buffered with 2 ml 40% w/v K_2HPO_4 solution and extracted with 15 ml ethylene dichloride containing 30% by volume of n-amyl alcohol as described previously (Misra et al 1971). Other details on extraction, liquid scintillation counting, estimation of free drug concentrations and total radioactivity have been described earlier (Misra et al 1971). The values of morphine metabolites (as morphine equivalents) were obtained by subtracting the values of extractable morphine per g tissue or ml fluid from the corresponding total radioactivity values.

Animal experiments. Male Wistar rats (160–190 g) were injected intravenously either with a 2 mg kg^{-1} dose of [6-^{3}H (N)]morphine or the combination of same dose of morphine with 6 mg kg^{-1} dose of tripelennamine. The animals (n = 6 each in control and experimental groups) were killed 15 min after intravenous injection and the blood drawn into heparinized Vacutainer tubes (Becton-Dickinson, Rutherford, N.J.) by cardiac puncture. The plasma was immediately obtained by centrifugation and quickly frozen. Tissues were rinsed with ice-cold saline, blotted in tissue paper, weighed, wrapped in aluminum foil and stored frozen until analysed. The tissues were homogenized in 0·5 M HCl to provide a 10% w/v homogenate and 2 ml aliquots analysed in duplicate for [^{3}H]morphine and total radioactivity. Plasma samples diluted 1 : 5 with distilled water were similarly analysed.

The statistical significance of differences was determined using Student's *t*-test.

Results

Concurrent i.v. administration of morphine and tripelennamine combination (2 and 6 mg kg^{-1} doses respectively) produced approximately 40% mortality in rats. Death was due to tonic–clonic seizures. The behaviour of animals injected with this combination was different from that manifested when either drug was given alone. Morphine (2 mg kg^{-1} i.v.)-treated animals showed analgesia, respiratory depression, Straub tail and behavioural sedation. The animals which received tripelennamine (6 mg kg^{-1} i.v.) showed cns excitation, rapid and laboured respiration, ataxia and no mortality. Animals receiving the two drugs in combination concurrently showed exaggerated behavioural responses, hyperactivity, Straub tail, tail lashing, tremors, stereotypy, rapid and laboured respiration and ataxia with subsequent depression and slow respiration lasting for 3 to 4 h. Doses of tripelennamine higher than 6 mg kg^{-1} given i.v. in combination with 2 mg kg^{-1} doses of morphine produced lethality in all animals within 2 to 3 min of injection.

Data on the comparative concentrations of [^{3}H]morphine in tissues and plasma of animals injected i.v. with [^{3}H]morphine or a combination of [^{3}H]morphine and tripelennamine appear in Table 1. The uptake of [^{3}H]morphine in brain of animals receiving the two drugs in combination was significantly higher than that

Table 1. Comparative concentrations† of morphine in plasma and selected tissues of rats after i.v. injection of a 2 mg kg^{-1} dose of [6-^{3}H(N)]morphine or a combination of 2 and 6 mg kg^{-1} doses of [6-^{3}H(N)]morphine and tripelennamine respectively.

	Morphine concn	
	Control (morphine)	Test (morphine–tripelennamine)
Brain	136 ± 11	180 ± 8*
Plasma	423 ± 38	412 ± 28
Liver	2209 ± 140	2184 ± 229

† Data represent mean ± s.e.m. values of free morphine (ng g^{-1} tissue or ml^{-1} fluid) from 6 animals in each group. The animals were killed 15 min after the i.v. injection and blood and tissues removed for analyses.

* Denotes significant difference from the control value at $P < 0·01$.

Table 2. Comparative concentrations† of total morphine metabolites in plasma and liver of rats after i.v. injection of 2 mg kg^{-1} dose of [6-^{3}H(N)]morphine or a combination of 2 and 6 mg kg^{-1} doses of [6-^{3}H(N)]morphine and tripelennamine respectively.

	Morphine metabolites concn	
	Control (morphine)	Test (morphine–tripelennamine)
Plasma	12·40 ± 0·57	12·89 ± 1·53
Liver	41·59 ± 1·77	37·27 ± 2·80

† Data represent mean ± s.e.m. values of morphine metabolites (μg-equivalents of morphine g^{-1} tissue or ml^{-1} fluid) from 6 animals in each group. The animals were killed 15 min after the i.v. injection and blood and tissue removed for analyses.

in the control morphine group. The concentrations of morphine in plasma and liver of animals receiving the 2 drugs in combination although somewhat lower than those in the control morphine group, were not significantly different. Brain to plasma morphine concentration ratio in morphine–tripelennamine group (0·45 ± 0·03) was significantly ($P < 0·05$) higher than that in the morphine group (0·33 ± 0·04). Liver to plasma morphine concentration ratio in morphine–tripelennamine group (5·28 ± 0·38) was not significantly different from that in morphine-control group (5·32 ± 0·29). Similarly comparative concentrations of total morphine metabolites (Table 2) in liver and plasma of animals receiving the 2 drugs in combination, were also not significantly different from the control group.

Discussion

The analysis of morphine in tissues and plasma of rats 15 min after i.v. injection of morphine or the combination of morphine and tripelennamine was undertaken because peak values of morphine in brain occurred at this time after i.v. injection in rats (Dahlström & Paalzow 1978). The higher brain morphine uptake and higher brain to plasma morphine concentration ratio of animals receiving morphine–tripelennamine combination compared with those receiving morphine alone, imply that the potentiation of opiate effects by antihistamine could be due in part to pharmacokinetic or pharmacodynamic factors. The concentration of morphine in the brains of animals receiving the morphine–tripelennamine combination roughly corresponds to that produced by a 4 mg kg^{-1} dose of morphine alone administered intravenously. Although the mechanisms by which the antihistamine enhances brain morphine uptake is not clear, it is conceivable that haemodynamic variables involving depressed cardiovascular function, reduced cardiac output, or cerebral fluid dynamics alter the blood-brain barrier permeability and lead to the delivery of a larger fraction of morphine to the brain after i.v. injection of morphine-tripelennamine combination. The increased permeability of the blood-brain barrier may apply not only to the opiate but to tripelennamine as well, in view of the reported significant decrease from 47 to 20 mg kg^{-1} i.p. in the LD50 of tripelennamine in mice when it was administered concomitantly with a non-lethal 40 mg kg^{-1} dose of pentazocine (Waller et al 1980). This however, remains to be determined. Additionally, tripelennamine has anticholinergic atropine-like properties as well as local anaesthetic activity (Showalter & Moore 1978) and blocks the re-uptake of noradrenaline into nerve endings thereby potentiating the catecholamine effects (Issac & Goth 1965). Large doses of tripelennamine and other antihistamines produce cns excitation and tonic–clonic seizures (Wyngaarden & Seevers 1951). These effects could also influence the striking potentiation of antinociceptive effects (Tagashira et al 1982) and toxicity (Waller et al 1980) observed with tripelennamine and pentazocine or morphine combination. In-vitro opiate receptor binding or guinea-pig ileum assay utilizing the inhibition of specific [^{3}H]naloxone binding have however shown (Shannon & Su 1982) no interaction of tripelennamine and pentazocine at the molecular level. The relative doses of tripelennamine and opiate is an important consideration in this interaction.

Recent work (Gupta et al 1982) has shown that methaqualone responses are also potentiated by another antihistamine diphenhydramine as a result of inhibition of hepatic mixed-function oxidase activity, which leads to a significant increase in biological half-life of methaqualone and a marked decrease in its elimination rate constant and metabolic clearance rate. Although the inhibition of metabolism of morphine by antihistamine could not be ruled out, the rapidity of the onset of toxicity or lethality with combination of tripelennamine and morphine administered intravenously would appear to minimize the role of metabolic factors in the toxicity of these drugs in combination.

The authors thank Dr S. J. Mulé for his kind interest. Tripelennamine hydrochloride (pyribenzamine hydrochloride) was a generous gift from CIBA-GEIGY Corporation, Summit, N.J.

REFERENCES

Bhargava, H. N. (1981) Clin. Toxicol. 18: 175–188

Burton, J. F., Zawadzkies, E. S., Wetherell, H. R., Moy, T. W. (1965) J. Forensic Sci. 10: 466–472

Dahlström, B. E., Paalzow, L. (1978) in. Adler, M. L., Manara, L., Samanin, R. (eds) Factors Affecting the Action of Narcotics. Raven Press, N.Y. pp 233–248

Gupta, K. P., Bhargava, K. P., Ali, B. (1982) J. Pharm. Pharmacol. 34: 744–746

Issac, L., Goth, A. (1965) Life Sci. 4: 1899–1904

Misra, A. L., Mitchell, C. L., Woods, L. A. (1971) Nature (London) 232: 48–50

Poklis, A. (1982) Drug Alc. Dependence 10: 257–267

Shannon, H. E., Su, T. P. (1982) Pharmacol. Biochem. Behav. 17: 789–795

Showalter, C. V., Moore, L. (1978) J. Am. Med. Assoc. 239: 1610

Szwed, J. J. (1970) Ann. Intern. Med. 73: 771–774

Tagashira, E., Kachur, J. F., Dewey, W. L. (1982) Pharmacologist 24: 188

Waller, D. P., Katz, N. L., Morris, R. W. (1980) Clin. Toxicol. 16: 17–23

Wendt, V. E., Puro, H. E., Shapiro, J., Mathews, W., Wolf, P. L. (1964) J. Am. Med. Assoc. 188: 755–759

Wyngaarden, J. B., Seevers, M. H. (1951) Ibid. 145: 277–281