De Boer et al (1980, 1981) have demonstrated that rectal administration reduces the hepatic first pass oxidative metabolism of propranolol and lignocaine in the rat. We have confirmed this phenomenon using phenol which undergoes extensive hepatic conjugation. Also our data indicates that intestinal first pass metabolism of phenol is partially if not completely avoided when the rectal route is employed. As discussed by De Boer et al (1982) it is unlikely that hepatic first pass metabolism can be completely by-passed using rectally administered drugs since only the inferior and middle haemorrhoidal veins drain into the vena cava. The superior haemorrhoidal vein feeds into the hepatic protal vein and there exists extensive anastomoses between all the rectal veins.

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Effect of diamorphine, Δ^9-tetrahydrocannabinol and ethanol on intravenous cocaine disposition

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The disposition of cocaine (1 mg kg^{-1}) was altered by diamorphine (0.1 mg kg^{-1}) and that of morphine (1 mg kg^{-1}) was altered after their concurrent administration as a bolus i.v. injection to rats by cocaine, without any changes in the metabolism of the drugs. Δ^9-Tetrahydrocannabinol (10 mg kg^{-1} i.p.) did not affect the cocaine disposition. Chronic ethanol treatment (2.5 g kg^{-1} orally twice daily for 16 days) produced a significantly higher brain-to-plasma cocaine concentration ratio than did saline as control, without any changes in cocaine metabolism.

Concomitant intravenous use of cocaine with diamorphine ("Speedballing") or with Δ^9-tetrahydrocannabinol (Δ^9-THC) or ethanol is currently popular with drug abusers. Aside from some work on the behavioural interaction of cocaine with morphine (Nott 1968), diamorphine (Pickett 1970). Δ^9-THC (Pryor et al 1976) or ethanol (Kissin 1974), no information is available on the drug dispositional aspects of these interactions. This investigation was undertaken to obtain this information.

Materials and methods

[^{3}H] Ring-labelled cocaine as prepared by Nayak et al, (1974) was diluted with non-radioactive cocaine hydrochloride to provide a specific activity of approximately 10 μCi mg^{-1}. All doses were expressed as free base. [6-^{3}H (N)] Morphine (specific activity 9.84 Ci m mol^{-1}) (New England Nuclear Corp, Boston, Mass.) was diluted with non-radioactive morphine hydrochloride to provide a specific activity of 10 μCi mg^{-1}. Diamorphine (heroin) was prepared in the laboratory by the acetylation of morphine base.

Δ^9-THC (0.5 ml) (from sealed ampoules of 1g/5 ml ethanol USP as supplied by the Research Triangle Institute through the courtesy of Dr. R. Hawks, NIDA, Rockville, Md.) was transferred to a volumetric flask (5 ml) and evaporated to dryness under nitrogen. The residue was resuspended in 10% v/v Tween 80 (0.5 ml) by thorough mixing in a vibro mixer and the solution diluted to 5 ml with 0.9% NaCl (saline). The final suspension (20 mg ml^{-1}) was transferred to a 5 ml amber multidose injection vial, and was freshly prepared.

Cocaine-diamorphine combination. Male Wistar rats (250–300 g) were injected i.v. either with a 1 mg kg^{-1} dose of [^{3}H]cocaine or a solution containing 1 mg kg^{-1} dose of [^{3}H]cocaine and 0.1 mg kg^{-1} dose of diamorphine. The animals were killed 10 min later and the

* Correspondence.

plasma and tissues analysed for [^{3}H]cocaine and total radioactivity (Nayak et al 1976).

Cocaine-[^{3}H]morphine combination. Male Wistar rats (180–200 g) were injected i.v. either with a 1 mg kg^{-1} dose of [^{3}H]morphine or a combination of the same dose each of [^{3}H]morphine and non-labelled cocaine. The animals were killed 15 min after injection and the plasma and tissues analysed for [^{3}H]morphine and total radioactivity (Misra et al 1971).

Cocaine-Δ^9-THC combination. Male Wistar rats (270–400 g) were injected i.p. either with the vehicle (1.0% v/v Tween 80 in saline) or 10 mg kg^{-1} Δ^9-THC in the vehicle. One hour after injection, 2.5 mg kg^{-1} [^{3}H] cocaine was injected i.v. to the two groups of 5 animals and these were killed 15 min later and the plasma and tissues analysed for [^{3}H]cocaine and total radioactivity. At 10 mg kg^{-1}, Δ^9-THC produced behavioural sedation within 10 min of injection, which lasted for about 1.5 h. Behaviourally sedated animals were markedly sensitive to external tactile and auditory stimuli.

Cocaine-ethanol combination. Male Wistar rats (120–160g) were given either water or a 2.5 g kg^{-1} dose of ethanol (20% w/v) orally twice daily (10 am, and 4 pm) for 16 days. On the 17th day, [^{3}H]cocaine 2.5 mg kg^{-1} was injected i.v. into the two groups of 8 animals. Five min later, water or a dose ethanol 2.5 g kg^{-1} was given orally to the two groups and 10 min later they were killed and the plasma and tissues analysed for [^{3}H]-cocaine and total radioactivity.

Results

Cocaine-diamorphine combination. The rats given the drugs in combination showed Straub tail, ataxia, motor incoordination and laboured breathing. The concentrations of cocaine in the brain, heart and lung in cocaine-diamorphine combination group were significantly lower than those in the cocaine group (Table 1). The values of cocaine in plasma and liver were not significantly different. The brain-to-plasma cocaine concentration ratio in the cocaine-diamorphine group (9.33 ± 0.38) was significantly ($P < 0.01$) lower than that in the cocaine group (12.21 ± 0.66). The liver-to-plasma cocaine concentration ratio in the combination group (1.96 ± 0.24) was not significantly different from that in the cocaine group (1.70 ± 0.25). There was no significant difference in the ratio of the concentrations of cocaine metabolites to unchanged drug in the liver in the two groups.

Table 1. Disposition[1] of cocaine[2] in rats injected i.v. (A) either with [^{3}H]cocaine or a combination of [^{3}H]cocaine and diamorphine, and disposition of morphine[3] in rats injected i.v. (B) either with [6-^{3}H(N]morphine or a combination of [6-^{3}H(N)]morphine and cocaine.

	Cocaine (A)		Morphine (B)	
Biofluid or tissue	Cocaine group	Cocaine-diamorphine combination group	Morphine group	Morphine-cocaine combination group
Plasma	111 ± 8	101 ± 4	432 ± 32	326 ± 38
Brain	1336 ± 41	941 ± 48**	56 ± 2	50 ± 1*
Heart	489 ± 35	368 ± 8**	400 ± 14	342 ± 17*
Lung	1535 ± 80	1092 ± 50**	839 ± 25	649 ± 27**
Liver	181 ± 20	198 ± 28	756 ± 121	885 ± 77

[1] Data represent mean ± s.e.m. (ng g^{-1} tissue or ml. fluid) from 5 rats in each group.
[2] Rats were killed 10 min after i.v. injection either of [^{3}H]cocaine (1 mg kg^{-1}) or a combination of 1 mg kg^{-1} [^{3}H]cocaine with 0.1 mg kg^{-1} diamorphine.
[3] Rats were killed 15 min after i.v. injection either of [^{3}H]morphine (1 mg kg^{-1}) or a combination of the same dose each of morphine and cocaine.
*,** denote significant differences from the corresponding values in the cocaine (A) or morphine (B) group at $P < 0.05$ and $P < 0.01$ respectively.

Cocaine-morphine combination. The concentrations of morphine in the brain, heart, and lung in the morphine-cocaine group were significantly lower than those in the morphine group (Table 1). The values of morphine in the liver although somewhat higher than in the morphine group were not significantly different. The brain-to-plasma morphine concentration ratio in the morphine-cocaine group (0.16 ± 0.02) was not significantly different from that in the morphine group (0.13 ± 0.01). The liver-to-plasma morphine concentration ratio in the morphine-cocaine group (2.81 ± 0.26) was significantly higher ($P < 0.05$) than that in the morphine group (1.79 ± 0.30). The values of morphine metabolites in plasma, heart, lung and liver and the ratios of the concentrations of morphine metabolites to unchanged drug in the liver were not significantly different in the two groups.

Cocaine-Δ^9-THC combination. There were no significant differences in the concentrations of cocaine in plasma, brain and liver in the two groups. The brain-to-plasma cocaine concentration ratio in the Δ^9-THC treated group (11.58 ± 0.59) was not significantly different from that in the cocaine control group (13.76 ± 1.41), like-wise the liver-to-plasma cocaine concentration ratio (1.52 ± 0.23) and the cocaine control group (1.27 ± 0.07). The values of cocaine metabolites in plasma and liver were also not significantly different in the two groups.

Cocaine-ethanol combination. The concentrations of cocaine in plasma, heart and lung in the ethanol-treated group were not statistically significantly different from those in the control group. The brain-to-plasma cocaine concentration ratio in the ethanol-treated group (11.26 ± 0.45) was significantly higher ($P < 0.05$) than that in the cocaine control group (9.46 ± 0.56). Liver-to-plasma cocaine concentration ratio in the ethanol-treated group (1.77 ± 0.19) was not significantly different from that in the cocaine control group (1.53 ± 0.19) nor were the concentrations of cocaine metabolites in plasma and liver or the ratio of cocaine metabolites to unchanged drug in plasma and liver (14.11 ± 0.99; 27.99 ± 2.73) and controls (12.22 ± 1.00; 31.99 ± 0.67) respectively.

Discussion

Cocaine is metabolized fairly rapidly to norcocaine, benzoylecgonine, benzoylnorecgonine, ecgonine

methyl ester and ecgonine as major metabolites (Nayak et al 1976). The t½β of cocaine in rat brain and plasma after i.v. injection was 0.4 and 0.3 h respectively (Nayak et al 1976). Diamorphine is also rapidly biotransformed to 6-acetylmorphine and subsequently to morphine (Way et al 1965). Diamorphine is 21 times more potent than morphine after i.v. injection in the rat, based on the peak effect, and 7 times more potent, based on the area under the time-action curves, for the warm water tail withdrawal test (Umans & Inturrisi 1981). Its respiratory depressant potency is also correspondingly greater than morphine. Preliminary experiments with different combinations of diamorphine and cocaine in a bolus i.v. injection showed a significant lowering of the LD50 of cocaine (17.5 mg kg^{-1}) in rats, a 0.2 or 0.3 mg kg^{-1} dose of diamorphine in combination with 3 mg kg^{-1} cocaine given i.v. proved lethal within 5 min of injection. The lethality was not due to the higher uptake of cocaine in the central nervous system of the rats as the concentrations of cocaine in brain and other tissues in the cocaine-diamorphine combination group were actually lower than those in the cocaine control group. Because peak values of morphine in brain occur 15 min after i.v. injection in rats (Dahlström & Paalzow 1978), the analysis of [^{3}H]morphine in morphine control and morphine-cocaine combination group was undertaken at this time. The concentrations of morphine in brain and some tissues in the cocaine-[^{3}H]morphine combination group were significantly lower than those in the morphine control group. Thus the disposition of cocaine is altered in the presence of diamorphine and the disposition of morphine by cocaine, when these drugs are administered in combination as a bolus i.v. injection. These alterations did not involve changes in the metabolism of these drugs. Narcotic agonists and cocaine markedly depress the medullary respiratory centre and when they are administered as a bolus i.v. injection, their additive effect could produce a fatal depression of the respiratory centre.

Cocaine disposition was not altered in rats pretreated with Δ^9-THC but those that received the two drugs in combination were sedated and did not show the usual stimulant effects of cocaine.

Acute administration of ethanol inhibits and chronic ethanol treatment enhances, the metabolism of other drugs by induction of hepatic microsomal enzymes (Misra et al 1971; Rubin & Lieber 1968; Kissin 1974). In animals chronically treated with ethanol, the brain to plasma cocaine concentration ratio was significantly higher than in controls. Lack of significant differences in the ratio of the concentration of cocaine metabolites to unchanged cocaine in liver and plasma in the two groups implied that the metabolism of cocaine was not affected by chronic ethanol treatment. Acute administration of a smaller dose of ethanol (0.4 g kg^{-1} orally) also did not affect the disposition of cocaine injected i.v. in rats (Misra et al, unpublished observations).

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