ment with those found for lignocaine in rats (De Boer et al 1980a).

From the literature it is known that oral absorption of propranolol is almost complete (Paterson et al 1970), but systemic availability is only 3%. No data are available about the extent of its rectal absorption. From our experiments it can be concluded that the rectal route of propranolol in rats is practically entirely a non-hepatic route, resulting in almost complete systemic availability.

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In vivo effect of toxic alkaloids on drug metabolism

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Although the involvement of hepatic drug-metabolizing enzymes in the biotransformation of nicotine (Booth & Boyland 1971; Tsujimoto et al 1972; Dohi et al 1973), colchicine (Schonharting et al 1973; 1974), and reserpine (Stitzel et al 1972; Stitzel 1974) has been reported, much less is known about the microsomal metabolism of boldine, brucine, emetine, sanguinarine, solanine and strychnine, and their effect on the biotransformation of other drugs. The present study reports on the comparative effect of these alkaloids on the alteration of the activity of hepatic drug-metabolizing enzyme system in rats.

The alkaloids, boldine, brucine suphate, colchicine, emetine hydrochloride, nicotine, reserpine, scopolamine hydrochloride and strychnine sulphate were purchased from Sigma Chemical Co., St. Louis, Mo., U.S.A. Sanguinarine nitrate was obtained from Aldrich Chemical Co., Milwaukee, Wis., U.S.A. Solanine was a generous gift from Dr T. J. Fitzpatrick, ARS-USDA, Philadelphia, Pa., U.S.A. All other chemicals used were analytical or reagent grade.

Male Sprague-Dawley rats (200–250 g) (Southern Animal Farms, Prattville, Alabama) were maintained in a temperature- and light-controlled room with access to Purina chow feed and tap water at all times except otherwise stated.

Groups of at least three animals were injected intraperitoneally with freshly made 0·9% NaCl (saline) solutions of brucine (2 mg kg^{-1}), colchicine (1 mg kg^{-1}), emetine (4 mg kg^{-1}), sanguinarine (10 mg kg^{-1}) and scopolamine (2 mg kg^{-1}). Boldine (5 mg kg^{-1}), nicotine (4 mg kg^{-1}), reserpine (2·5 mg kg^{-1}). solanine (10 mg kg^{-1}) or strychnine (2 mg kg^{-1}) was suspended in corn oil (Mazola brand) and administered intraperitoneally to the respective groups. The two control groups were injected with saline or corn oil. Injections were given daily for three successive days and the animals were used to determine pentobarbitone sleeping time or killed to isolate liver microsomes 24 h after the last injection. In an experiment designed to assess the effect of the alkaloids on the ability of phenobarbitone to induce hepatic microsomal enzymes, animals were given an alkaloid and phenobarbitone sodium (75 mg kg^{-1}, i.p.) simultaneously for three successive days, and killed on the fourth day to isolate liver microsomes (Dalvi & Robbins 1978).

To determine whether the alkaloids possess microsomal enzyme-inducing or -inhibiting properties, pentobarbitone sleeping times were measured in the rats according to Dalvi & Howell (1977).

The cytochrome P-450 content of the microsomal preparations was determined by the procedure of Omura & Sato (1964). The ability of microsomal enzymes isolated from treated and untreated rats to metabolize drugs was examined using benzphetamine and aniline as substrates (Dalvi & Howell 1977). The amount of protein in each sample was estimated using biuret method modified to include deoxycholate in samples (Dalvi et al 1974).

Table 1. Effect of pretreatment of the alkaloid compounds on pentobarbitone sleeping time in rats.

Compound	Dose (mg kg^{-1})	Sleeping time (% of control)
Boldine	5	113
Brucine	2	72
Colchicine	1	208
Emetine	4	122
Nicotine	4	53
Reserpine	2·5	202
Sanguinarine	10	272
Scopolamine	2	85
Solanine	10	275
Strychnine	2	73

* Correspondence.

Table 2. Effect of pretreatment of the alkaloid compounds on hepatic drug-metabolizing enzyme system in rats.

Compound	Benzphetamine *N*-demethylase activity (nmol formaldehyde min^{-1} mg^{-1} protein)*	Aniline hydroxylase activity (nmol *p*-aminophenol min^{-1} mg^{-1} protein)*	Cytochrome P-450 (nmol mg^{-1} protein)*
Control (oil)	3·57 ± 0·05	0·405 ± 0·054	0·60 ± 0·01
Control (saline)	3·72 ± 0·30	0·413 ± 0·011	0·53 ± 0·09
Boldine	3·96 ± 0·86	0·420 ± 0·005	0·56 ± 0·01
Brucine	3·83 ± 0·64	0·391 ± 0·063	0·54 ± 0·02
Colchicine	3·68 ± 0·23	0·410 ± 0·053	0·62 ± 0·07
Emetine	2·21 ± 0·29	0·239 ± 0·033	0·37 ± 0·01
Nicotine	4·31 ± 0·80	0·616 ± 0·037	0·74 ± 0·06
Reserpine	3·18 ± 0·15	0·745 ± 0·171	0·72 ± 0·06
Sanguinarine	2·19 ± 0·41	0·268 ± 0·032	0·41 ± 0·03
Scopolamine	3·91 ± 0·34	0·500 ± 0·010	0·68 ± 0·09
Solanine	3·07 ± 0·02	0·356 ± 0·023	0·42 ± 0·02
Strychnine	3·20 ± 0·10	0·415 ± 0·069	0·54 ± 0·01

* Mean ± s.e. of the mean of observations from three animals.

Table 3. Effect of the alkaloid compounds on induction by phenobarbitone (75 mg kg^{-1}) of hepatic microsomal enzymes in rats.

Treatment	Benzphetamine *N*-demethylase activity (nmol formaldehyde min^{-1} mg^{-1} protein)*	Aniline hydroxylase activity (nmol *p*-aminophenol min^{-1} mg^{-1} protein)*	Cytochrome P-450 (nmol mg^{-1} protein)*
Control (saline)	3·89 ± 0·36	0·455 ± 0·020	0·64 ± 0·03
Control (Oil)	3·63 ± 0·12	0·417 ± 0·041	0·62 ± 0·02
PB	8·68 ± 0·21	0·543 ± 0·034	1·81 ± 0·10
Boldine	4·83 ± 0·33	0·375 ± 0·026	0·63 ± 0·03
PB + Boldine	9·05 ± 0·67	0·670 ± 0·048	1·84 ± 0·09
Brucine	3·98 ± 0·03	0·461 ± 0·029	0·68 ± 0·05
PB + Brucine	9·08 ± 0·21	0·555 ± 0·038	1·87 ± 0·07
Colchicine	4·32 ± 0·15	0·396 ± 0·027	0·70 ± 0·05
PB ± Colchicine	9·35 ± 0·51	0·463 ± 0·067	1·52 ± 0·10
Emetine	2·41 ± 0·23	0·280 ± 0·046	0·50 ± 0·06
PB + Emetine	7·20 ± 0·37	0·435 ± 0·012	1·48 ± 0·06
Nicotine	4·11 ± 0·29	0·577 ± 0·024	0·93 ± 0·04
PB + Nicotine	11·24 ± 0·47	0·808 ± 0·051	2·21 ± 0·11
Reserpine	4·90 ± 0·27	0·810 ± 0·047	0·87 ± 0·03
PB + Reserpine	10·23 ± 0·70	0·952 ± 0·061	2·32 ± 0·09
Sanguinarine	2·03 ± 0·05	0·206 ± 0·032	0·38 ± 0·04
PB + Sanguinarine	7·22 ± 0·23	0·461 ± 0·021	1·52 ± 0·14
Scopolamine	4·75 ± 0·12	0·490 ± 0·020	0·58 ± 0·05
PB ± Scopolamine	8·53 ± 0·30	0·585 ± 0·029	1·77 ± 0·06
Solanine	3·43 ± 0·14	0·399 ± 0·010	0·54 ± 0·03
PB + Solanine	9·21 ± 0·31	0·567 ± 0·022	1·76 ± 0·08
Strychnine	4·62 ± 0·22	0·423 ± 0·017	0·81 ± 0·02
PB + Strychnine	11·44 ± 0·57	0·759 ± 0·035	2·20 ± 0·09

* Mean ± s.e. of the mean of observations from three animals.

The data in Table 1 indicate that compared with the control there was an increase in the pentobarbitone sleeping time in rats pretreated with boldine, colchicine, emetine, reserpine, sanguinarine and solanine suggesting these compounds to be inhibitors of microsomal enzymes. It has been reported by Schonharting et al (1974) that the microsomal metabolism of colchicine is enhanced after induction by colchicine itself. We found both colchicine and reserpine treatments resulted in diarrhoea and fluid loss as well as in decreased food consumption by the exposed animals. Thus, starvation of the colchicine- and reserpine-treated animals may have been a cause of increased sleeping time due to decreased pentobarbitone metabolism (Kato & Gillett 1965). The prolonged sleeping time seen in rats pretreated with emetine may be attributed to the direct inhibition of microsomal enzymes by this alkaloid or its metabolites (Miller et al 1970).

In contrast to the enzyme inhibition caused by those alkaloids, strychnine, brucine, nicotine and scopolamine appear to be inducers of drug-metabolizing enzymes. Strychnine is a substrate for microsomal enzymes (Kato et al 1964) and it is possible that it and brucine may have the ability to induce biotransformation enzymes, thus decreasing the pentobarbitone sleeping time. Although Westfall & Brase (1971) reported nicotine to lack inducing properties, our data and those of Yamamoto et al (1966) and Wenzel & Broadie (1966) indicate that this alkaloid is an inducer of microsomal enzymes.

In another experiment, rats were treated with the alkaloids in a similar way to that in the previous experiment to study drug metabolism in vitro. The results on the determination of cytochrome P-450 content and the activity of benzphetamine *N*-demethylase and aniline hydroxylase in hepatic microsomes isolated from the animals are presented in Table 2, which shows that there was a distinct decrease in the activity of benzphetamine *N*-demethylase and aniline hydroxylase, and the concentration of cytochrome P-450 in liver microsomal preparations from rats pretreated with emetine and sanguinarine. But the increase in cytochrome P-450 and aniline metabolism observed in liver microsomes from the rats exposed to nicotine, scopolamine and reserpine confirms the fact that nicotine and scopolamine are inducers of the enzyme system and starvation may have been a factor in the reserpine-induced increased enzyme activity (Stitzel 1974). The results further indicated that solanine tended to inhibit the microsomal enzymes whereas pretreatment of rats with boldine, brucine, colchicine and strychnine did not have appreciable effect on in vitro drug metabolism.

Another experiment was made to examine whether alkaloid treatment altered the induction of microsomal enzymes by phenobarbitone. Only emetine and sanguinarine impaired the process of hepatic microsomal enzyme induction. On the other hand, nicotine, reserpine and strychnine appear to potentiate the inducing properties of phenobarbitone. In conclusion, except emetine, sanguinarine and to some extent nicotine, all other alkaloids failed to show decisively that they are inhibitors or inducers of microsomal enzymes at the concentrations used in these studies. Of these alkaloids, boldine, emetine, nicotine, reserpine and sanguinarine, are type II compounds (Peeples & Dalvi 1977) and these so-called type II compounds which react with the 6th ligand of the heme of cytochrome P-450 seem, with the exception of nicotine, to lack real inducing properties. Compounds capable of acting as microsomal enzyme inducers tend to produce type I spectra (Mannering 1971). Furthermore, these alkaloids may be degraded very rapidly by the drug-metabolizing enzymes, never to achieve the concentration necessary for induction or inhibition of the enzymes because of their high toxicity.

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