to be the most efficient method of medicament application to a tablet core. Nearly 100% quinine hydrochloride recovery was obtained with this method.

8. Of the three methods investigated, the air-atomized coating system showed the greatest loss of medicament. The airless-spray-coating system showed hardly any loss of medicament. The conventional coating procedure was intermediate in medicament content with respect to the atomized systems.

From this study there appears to be an advantage in applying medication by the airless-spray system. Such a system eliminates the excess medication which must be added in the conventional coating procedure and would thus result in a savings in labor and material.

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Keyphrases

Core tablets—drug coating
Physical parameters, effect—coating core tablets
Powder, sucrose–acacia solution—coating
Drug–diluent ratio, effect—core coating
Film coating—airless-spray, air-atomized systems

Notes

Enhanced Mortality of Selected Central Nervous System Depressants in Hypoexcretory Mice

By B. A. BECKER, K. L. HINDMAN*, and J. E. GIBSON

The mortality of nine central nervous system depressant drugs was compared in normal and hypoexcretory mice. Anuria was produced in mice by penile ligation; cholestasis was produced by bile duct ligation. The intraperitoneal administration of prochlorperazine, trifluoperazine, perphenazine, meprobamate, and chloral hydrate produced significantly elevated mortality rates in anuric mice whereas promazine, perphenazine, and meprobamate showed elevated mortality rates in cholestatic mice. The mortality of chlorpromazine and phenobarbital was not altered in hypoexcretory mice.

CHOLESTATIC OR anuric mice may be more susceptible to some pharmacologic agents than mice without excretory impairment as shown by Gibson and Becker (1). In that work the acute lethality of ouabain was found to be enhanced in cholestatic mice; digoxin and digitoxin had higher mortality rates in anuric mice. Possible alteration in acute lethality of nine central nervous system depressant drugs were similarly studied in cholestatic and anuric mice: five phenothiazine tranquilizers (Table I) including two from the propyldimethylamine subgroup, promazine and chlorpromazine; three from the propylpiperazine subgroup, prochlorperazine, trifluoperazine, and perphenazine; the nonphenothiazine tranquilizer, meprobamate; and three sedative-hypnotics, pentobarbital, phenobarbital, and chloral hydrate.

METHODS

Male Swiss-Webster mice weighing 25–40 Gm. and allowed free access to food and water throughout the experiment were rendered anuric by penile ligation under light ether anesthesia by the method of Becker and Gibson (2). Cholestasis was induced by ligation of the common bile ducts of other male mice of the same strain under ether anesthesia. The surgical wound was closed by 9-mm. wound clips. The general experimental procedure followed that previously reported (1). Preliminary experiments were performed on intact mice to determine suitable dosages of the test agents. Since the anticipated responses were enhancement or no change in mortality rates, dosages were sought which would be in the low lethal range, *e.g.*, LD_{10}–LD_{50}, as enhancement of mortality rates by dosages in the high lethal range, LD_{50}–LD_{99}, would be difficult to demonstrate with any degree of statistical confidence. The selected drugs were administered intraperitoneally in aqueous solution or 0.5% sodium carboxymethylcellulose suspension. The desired dosage of the selected agent was administered 2 hr. after penile ligation (PL) or 24 hr. after bile duct ligation (BDL); sham-operated animals, similarly treated, served as standards. Vehicle-treated operated and sham-operated mice served as controls. Since none of the control animals died under the conditions used, control data were eliminated from

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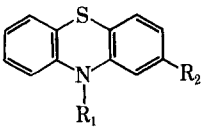
TABLE I—STRUCTURE OF PHENOTHIAZINE COMPOUNDS TESTED



Name	R_1	R_2
Subgroup A. Propyldimethylamine		
Promazine	$-CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	H
Chlorpromazine	$-CH_2-CH_2-CH_2-N(CH_3)_2$	Cl
Subgroup B. Propylpiperazine		
Prochlorperazine	$-CH_2-CH_2-CH_2-N$ piperazine $-CH_3$	Cl
Trifluoperazine	$-CH_2-CH_2-CH_2-N$ piperazine $-CH_3$	CF_3
Perphenazine	$-CH_2-CH_2-CH_2-N$ piperazine $-CH_2-OH$	Cl

the results. The percent kill was recorded 12 hr. after drug administration to PL mice and 24 hr. after drug treatment of BDL mice. The 12-hr. observation period was selected in the case of PL mice as previous studies had uniformly shown PL mice to survive for more than 18 hr. before succumbing to the effects produced by anuria; a 24-hr. observation period was unsuitable because approximately 30% of PL mice died in that period (2). Standard errors of the percent kill and statistical significance ($p<0.05$) of differences in percent kill between hypoexcretory and standard groups were determined by the binomial expansion method (3).

RESULTS

In cholestatic mice, the 24-hr. acute mortality was significantly enhanced when the animals were treated with dosages of promazine, perphenazine, or meprobamate (Table II).

The agents which exhibited significantly elevated mortality rates in anuric mice were: prochlorperazine, trifluoperazine, perphenazine, meprobamate, and chloral hydrate (Table II).

Pentobarbital but not phenobarbital had significantly reduced mortality rates in either anuric or cholestatic mice (Table II).

DISCUSSION

Increase in the mortality rates of pharmacologic agents in hypoexcretory animals is presumably the consequence of the inability to excrete the agent or metabolic products. The metabolic products may be toxic, or on the other hand, accumulation of nontoxic metabolites may contribute to enhanced mortality rates by preventing the metabolic alteration of the parent substance according to the law of mass action.

Examination of the results presented in Table II reveals two agents, meprobamate and perphenazine, whose mortality rates are increased when either urinary or biliary excretion is impaired, suggesting that these compounds may be excreted by both major excretory routes in mice. The results also show an interesting structure-action correlation among the phenothiazines (Table I). Phenothiazines with propylpiperazine moieties are uniformly more toxic when the urinary route of excretion is blocked while the propyldimethylamine subgroup is not so affected. When the biliary route of excretion is impaired, the phenothiazines affected, promazine and perphenazine, are found to belong to different subgroups with respect to both N substitution and ring substitution (Table I).

Little is known of the metabolism and excretion of the phenothiazine compounds in the mouse. In man, rats, and dogs, however, the metabolism and excretion of the phenothiazines has been the subject of considerable investigation. The metabolism of the phenothiazines is extensive and the role of

TABLE II—PERCENT MORTALITY OF CNS DEPRESSANTS IN CHOLESTATIC AND ANURIC MICE

Drug	Dose[a] mg./Kg.	Cholestatic[b] Operated No.	Cholestatic[b] Operated % ± S.E.[d]	Cholestatic[b] Sham-operated No.	Cholestatic[b] Sham-operated % ± S.E.[d]	Anuric[c] Operated No.	Anuric[c] Operated % ± S.E.[f]	Anuric[c] Sham-operated No.	Anuric[c] Sham-operated % ± S.E.[f]
Promazine	40	29	21 ± 8	35	6 ± 4[e]	28	7 ± 5	33	6 ± 4
Chlorpromazine	100	34	41 ± 8	32	33 ± 8	34	56 ± 9	33	55 ± 9
Prochlorperazine	50	33	24 ± 7	31	10 ± 5	24	42 ± 10	23	9 ± 6[e]
Trifluoperazine	200	39	56 ± 8	41	54 ± 8	34	91 ± 5	32	66 ± 8[e]
Perphenazine	21	34	56 ± 9	34	15 ± 6[e]	24	21 ± 8	3	3 ± 3[e]
Meprobamate	390	22	32 ± 10	21	5 ± 5[e]	31	39 ± 9	33	8 ± 5[e]
Pentobarbital	88	33	3 ± 3	35	20 ± 7	11	0	11	46 ± 15
Phenobarbital	13	13	39 ± 14	8	25 ± 15	12	36 ± 14	11	36 ± 14
Chloral hydrate	690	12	25 ± 13	12	25 ± 13	33	64 ± 8	32	41 ± 9[e]

[a] By intraperitoneal administration. [b] Mice rendered cholestatic by common bile duct ligation 24 hr. before drug administration. [c] Mice rendered anuric by penile ligation 2 hr. before drug administration. [d] Percent dead ± standard error 24 hr. after drug administration. [e] Significantly enhanced lethality of operated *vs.* sham-operated mice ($p < 0.05$). [f] Percent dead ± standard error 12 hr. after drug administration.

metabolism in the excretion of these compounds is recognized (4). The excretion of chlorpromazine in rats is divided equally between the urinary and biliary routes, the major routes of drug excretion. Only about 12% of the original dose of chlorpromazine is recovered in the urine as the unchanged drug, whereas the remainder is present as metabolites (5). In the present study cholestasis or anuria did not increase the lethality of chlorpromazine in mice, indicating that either the urinary or biliary route of excretion may serve adequately to remove chlorpromazine and its metabolites in mice.

In contrast to chlorpromazine, promazine is excreted primarily in the urine (70–80%) by the rat with the remainder excreted *via* the feces (6). Under these conditions it might be expected that the mortality of animals treated with a toxic dose of promazine might be enhanced if the urinary route of excretion were blocked. In mice, however, it was observed that the lethality was enhanced if the biliary route of excretion was blocked. This finding suggests that the primary excretory route of promazine and its metabolites may be different in mice than in rats or that a toxic metabolite of promazine is excreted primarily *via* the biliary route.

Phenothiazines having propylpiperazine moieties may be mainly excreted in the bile. In rats, triethylperazine, a propylpiperazine derivative of phenothiazine, is excreted largely in the bile with less than 10% of the dose appearing unchanged in the urine when given either orally or parenterally (7). The enhanced lethality of these compounds in anuric mice (Table II), however, may indicate that the urinary route of excretion for these compounds is more important in mice than in rats. Perphenazine appears to be dependent upon the function of both the urinary and biliary excretory routes in mice for detoxication since blockade of either route significantly increased the acute lethality of the compound.

Meprobamate is metabolized *in vivo* to hydroxymeprobamate, a pharmacologically inactive and nontoxic product. Both meprobamate and hydroxymeprobamate are conjugated with glucuronic acid and excreted *via* the urinary route in dogs (8). Ten percent of administered meprobamate is excreted unchanged and the remainder is excreted as metabolite in the urine. In mice the lethality of meprobamate is significantly enhanced when either the urinary or biliary routes of excretion is blocked (Table II). Since meprobamate and its metabolites are almost exclusively excreted by the kidneys in other species, the enhanced lethality of meprobamate in cholestatic mice is somewhat surprising. One explanation is that the mouse metabolizes or excretes meprobamate very differently from other mammalian species. Another possible explanation may be inhibition of meprobamate metabolism in the liver due to bile duct ligation thus resulting in delayed detoxication of the drug.

Chloral hydrate is reduced *in vivo* primarily to trichloroethanol, an active metabolite, and partially to trichloroacetic acid, an inactive metabolite. Both metabolic products may be conjugated with glucuronic acid and excreted either in urine or, to a smaller extent, bile (9). In mice, the acute lethality of chloral hydrate is increased by the anuric condition which correlates well with metabolism and excretion of chloral hydrate in man.

The significant reduction of lethality rates seen in hypoexcretory mice treated with pentobarbital but not phenobarbital cannot be readily explained. One possibility is that metabolites of pentobarbital accumulate in the blood of hypoexcretory animals and affect the equilibrium of pentobarbital toward increased tissue storage. Increased metabolism due to induction of liver microsomal enzymes is not believed to be an important factor in view of the short time (12 or 24 hr.) available for enzyme induction by pentobarbital. If enzyme induction were a significant mechanism, phenobarbital would also be expected to show a protective effect.

The dearth of information concerning metabolism and excretion of drugs in the mouse is not limited to the phenothiazines. Very little data of this type can be found in the literature. The authors are aware that extrapolation from one species to another is hazardous and must be done with great care. The above comments on metabolism and excretion in other species are germane to the findings described only if the metabolism and excretion of the drugs discussed are qualitatively the same in the mouse as in the other species.

The procedures employed in this study are relatively simple and can be carried out in a reasonable number of animals in a short time. The information gained from such procedures may prove to be of value in predicting the route of excretion of the drugs and/or their biotransformation products, and possible toxic reactions in the presence of reduced liver or kidney function. Such data may be of value in the safety evaluation of new drugs.

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Keyphrases

Hypoexcretion—mortality effect, mice
CNS depressants—test drugs
Anuria—penile ligation
Cholestasis—bile duct ligation