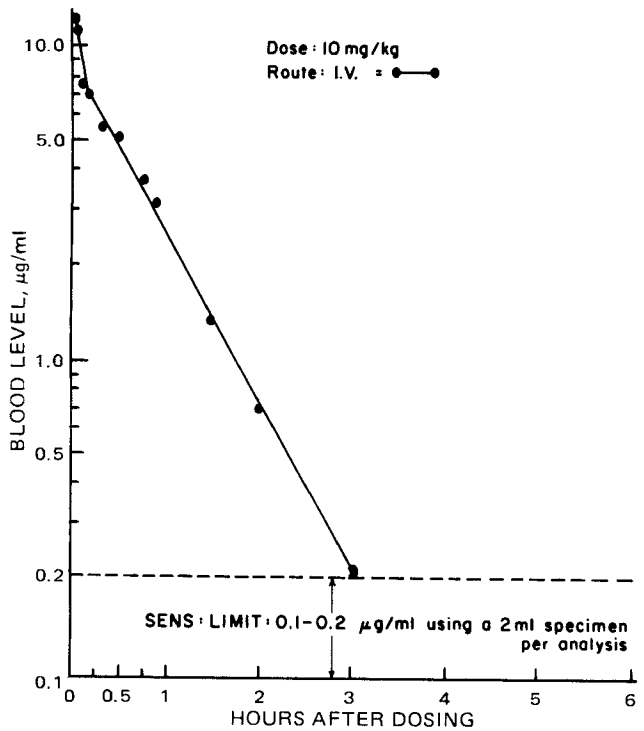

Figure 4—*Blood level curves of I in a dog following the administration of a single 10-mg/kg iv dose of I hydrochloride.*

I hydrochloride. The blood levels of the intact drug I (Fig. 4) showed a biphasic fall-off pattern with an apparent half-life of elimination of about 30 min. Urinary excretion of the parent drug accounted for only 0.1% of the administered dose, present mainly as a glucuronide–sulfate conjugate. No measurable levels of II were seen in either the blood or urine. The utility of the assay was demonstrated in the evaluation of the biopharmaceutic and pharmacokinetic profile of the drug in the dog[13].

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[x] To whom inquiries should be directed.

Oxidative Reactions of Hydroxylated Chlorpromazine Metabolites

RICHARD L. McCREERY

Abstract □ The oxidation pathways of two hydroxylated chlorpromazine metabolites were investigated using modern electrochemical techniques. Upon oxidation, the 7-hydroxy derivative of chlorpromazine rapidly reacts to form the 7,8-dihydroxy derivative and a substituted quinone. The oxidation potentials for both compounds were determined in the pH 3–8 range. The importance of these redox reactions and potentials to the pharmacology of the materials is discussed.

Keyphrases □ Chlorpromazine metabolites—oxidation pathways, electrochemical study, pH 3–8 □ Oxidation pathways—hydroxylated chlorpromazine metabolites, electrochemical study, pH 3–8 □ Electrochemistry—study of oxidation pathways of hydroxylated chlorpromazine metabolites □ Tranquilizers—chlorpromazine metabolites, electrochemical study of oxidation pathways

The widespread use of phenothiazine derivatives in the treatment of mental illness has inspired a large amount of research on their chemical properties and reactions. Of relevance to the present discussion are studies of the importance of redox reactions to the metabolism and mode of action of chlorpromazine and related neuroleptic drugs.

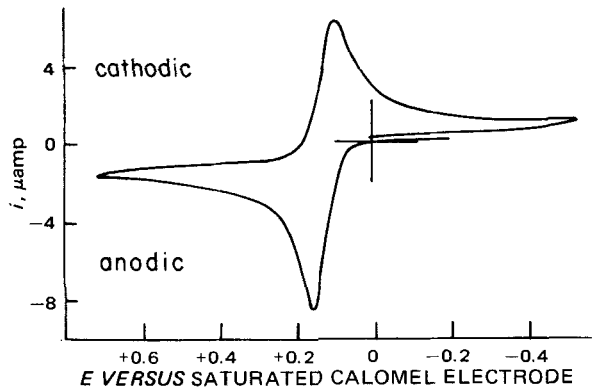


Figure 1—*Cyclic voltammogram of 5 × 10^{-4} M II in pH 4 McIlvaine buffer (carbon paste electrode; scan rate = 0.10 v/sec).*

The one-electron oxidation product of chlorpromazine, its cation radical, has been associated with membrane interactions that may be responsible for the drug's effect (1), and the radical has been suggested as a metabolic intermediate in the formation of chlorpromazine sulfoxide and hydroxylated chlorpromazine metabolites (2).

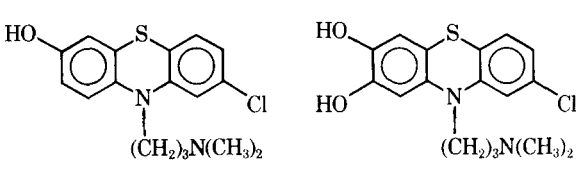
BACKGROUND

More recent investigations involved the importance of two hydroxylated metabolites of chlorpromazine to the beneficial and toxic effects of chlorpromazine therapy. The 7-hydroxy derivative of chlorpromazine (I) has pharmacological effects comparable to chlorpromazine in animal tests and has been suggested as the active form of the drug in neuroleptic therapy (3). In addition, the 7-hydroxy compound has been associated with the corneal opacity and skin pigmentation that occur in 5–25% of the patients receiving chlorpromazine chronically (4, 5). The 7,8-dihydroxy derivative of chlorpromazine (II) is also a metabolite of chlorpromazine in humans (6) and is a strong candidate for an agent producing toxic side effects. It also causes corneal opacity in rabbits (5) and has pronounced effects on mitochondrial membranes (7) and Na^+–K^+-dependent adenosine triphosphatase (8).

It is important to consider the possible role of oxidation in the metabolism and side effects of chlorpromazine. Oxidation of II by molecular oxygen produces hydrogen peroxide, the superoxide ion, and hydroxyl radicals (9). Heikkila *et al.* (9) suggested that this oxidation and the accompanying generation of reactive species are responsible for the neurotoxicity of the dihydroxy compound. In addition, it has been proposed that oxidation and polymerization of II result in the purple pigmentation of the skin or corneal opacity observed in chronic chlorpromazine patients. A further effect of II may be degeneration of nerve tissue, similar to that caused by 6-hydroxydopamine. The mechanism of neurotoxicity of the 6-hydroxy derivative of dopamine remains an active subject of research, but the ease of oxidation is important for its effects. Information about the oxidation potential of II would be useful in appraising its possible chemical similarity to the 6-hydroxy derivative of dopamine.

Although photoxidation of I has been associated with skin pigmentation, the reaction is not well characterized (4). The mushroom tyrosinase-catalyzed oxidation of I generates the dihydroxy derivative, as shown by UV and electron spin resonance spectra (10).

The work described here was undertaken to clarify the oxidative reactions of chlorpromazine, I, and II in solutions near physiological pH. Hopefully, information about oxidation potentials and reaction mechanisms will clarify the role of hydroxylated chlorpromazine metabolites in the toxic and beneficial effects of chlorpromazine therapy. The electrochemical results show that II is oxidized at a potential near that of the 6-hydroxy derivative of dopamine and that the product is stable on the time scale used here. Compound I rapidly undergoes further reaction upon oxidation to yield II and a quinone intermediate. The results provide an overall picture of the oxidation pathways of these compounds consistent with previously reported observations.



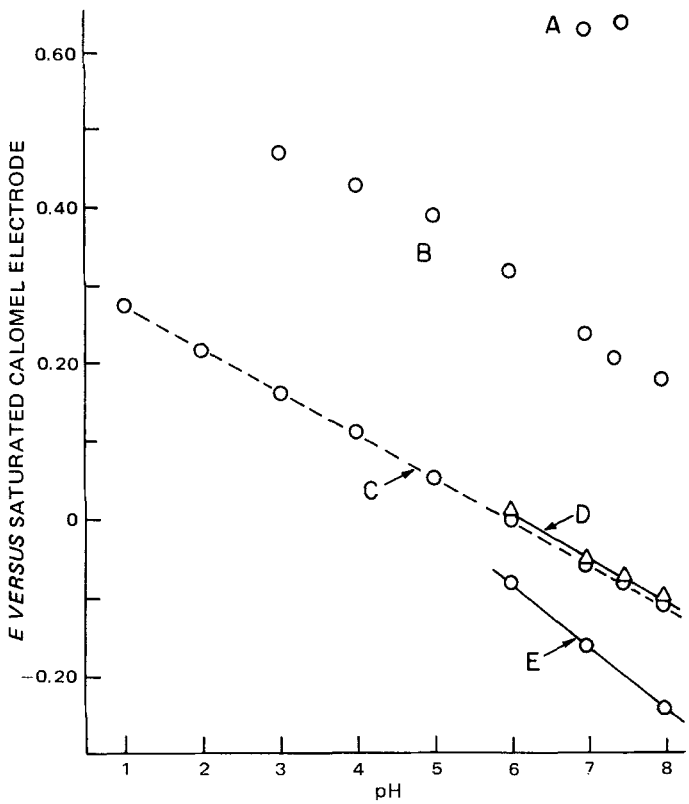


Figure 2—*Potential* versus *pH profiles for chlorpromazine and two hydroxylated metabolites. Key: A, $E_{p/2}$ for chlorpromazine; B, $E_{p/2}$ for I; C, $E_{p/2}$ for II; D, $E^{o'}$ for II; and E, $E^{o'}$ for dopamine 6-hydroxy derivative. Voltammograms were obtained using a carbon paste electrode. $E^{o'}$ values are midpoint potentials for titrations with the ferricyanide ion using a platinum indicator electrode.*

EXPERIMENTAL

All voltammetric experiments with scan rates below 0.5 v/sec were performed with an operational amplifier potentiostat of conventional design (11). A 27.9 × 35.5-cm (11 × 14-in.) *x–y* recorder was used to record slow scan voltammograms. Large-scale electrolysis was performed using a more powerful potentiostat based on a 50-w power amplifier. A 25.4-cm (10-in.) strip-chart recorder was used to record electrolysis current. High speed (above 0.5 v/sec) voltammograms were performed with a fast rising potentiostat interfaced to a laboratory scale minicomputer. The system allowed control of high speed experiments, with sampling of current occurring at a maximum rate of 200 kHz. The resultant voltammograms were displayed on an *x–y* oscilloscope monitor.

Electrochemical cell design was conventional and utilized a carbon paste working electrode, platinum wire auxiliary electrode, and saturated calomel reference electrode (12). To avoid any question about electrode fouling from electrolysis products, a new carbon paste surface was prepared for each voltammetric scan. To conserve the supply of phenothiazine derivatives, cell volume was limited to 1.5 ml; typical experiments consumed 400–600 μg of electroactive material. McIlvaine buffers made from 0.2 *M* Na_2HPO_4 and 0.1 *M* citric acid were utilized in the pH 3–8 range. Phosphate buffer, 0.2 *M*, at pH 2 and 0.1 *M* HCl were used below pH 3. In many cases, phenothiazines were dissolved with a few drops of 10^{-3} *M* HCl before addition of the buffer solutions.

Chlorpromazine hydrochloride[1], I[2], and III[2] were used without further purification.

[1] Courtesy of Dr. R. N. Adams, University of Kansas.
[2] Courtesy of Dr. A. A. Manian, Psychopharmacology Research Branch, National Institutes of Health.

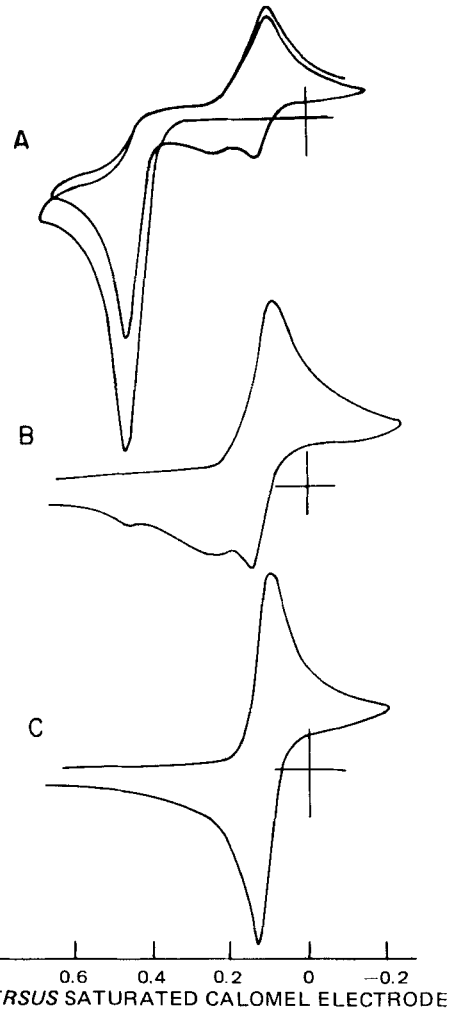


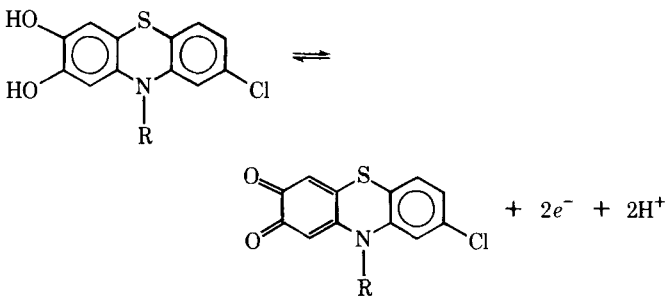
Figure 3—*Voltammograms before and during the coulometric oxidation of 554 μg of I in 3 ml of pH 4 McIlvaine buffer. Key: A, before electrolysis was initiated* (n = *0); B,* n = *3.2; and C,* n = *4.02.*

RESULTS

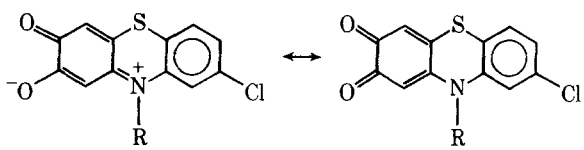
The electrochemistry of II was the simplest of the three compounds studied. Figure 1 shows the nearly reversible, well-defined voltammetric wave of II at pH 4. A similar wave was observed from pH 1 to 8, with the only effect of pH being a shift in the oxidation potential. Figure 2 includes a graph of the half-peak potential of the anodic wave *versus* pH. The plot is linear from pH 1 to 8, with a slope of 0.056 v/pH unit, indicating that the number of protons and electrons involved in the oxidation process is equal. The linearity of the pH profile for II below pH 4 was unexpected, since the reported value for the pKa of the thiazine nitrogen is 3.4 (13). Unless the pKa for the thiazine nitrogen is the same for both the oxidized and reduced forms of II, one would expect a change in slope in the $E_{p/2}$ *versus* pH profile in the region of pH 3.4.

After considering the pKa's of diphenylamine (0.79) and the 3-hydroxy derivative of phenothiazine (−2) (14), one has reason to doubt the published value of 3.4. The inconsistency may arise from the possibility that the value of 3.4 represents the titration of free hydrogen ions rather than the protonated thiazine nitrogen, in light of the fact that the investigators reporting that value started with a 10^{-3} *M* solution of II. Potentiometric titrations of II with ferricyanide yielded an average *n* value of 1.93 electrons per molecule in the pH 6–8 region. Titrations below pH 6 were not possible because the redox potential of ferricyanide is too low. The $E^{o'}$ values derived from these titrations are also plotted in Fig. 2. Coulometry of II at a carbon cloth electrode confirmed the value of two electrons per molecule for the oxidation. The UV–visible spectra of oxidized material agree well with those published by Grover *et al.* (10), with peaks at 262 and 508 nm. The molecular implications of these bands were discussed previously (15).

A cyclic voltammogram of I at pH 4 is shown in Fig. 3A. The voltammograms in the pH 3–8 range were qualitatively similar, with the only



Scheme I

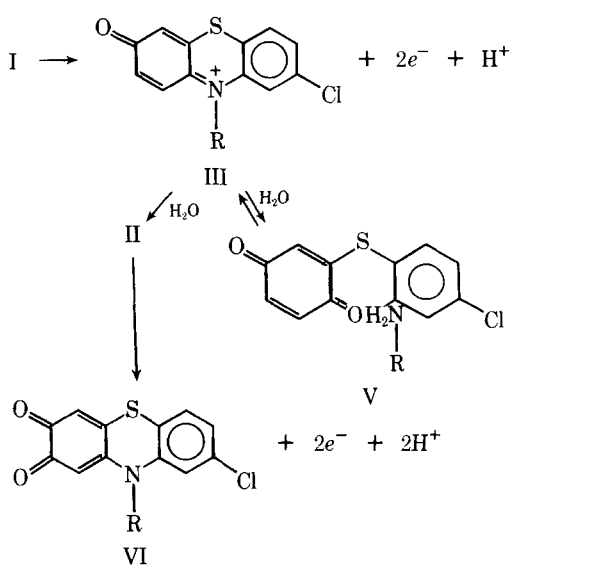


Scheme II

change being in the positions and magnitudes of the peaks. Figure 2 shows a plot of the half-peak potential for the major anodic peak as a function of pH. The cathodic peak shifted with pH in a fashion identical to the dihydroxy derivative. Since the oxidation of I is chemically irreversible, no attempt was made to titrate it potentiometrically. Coulometry of I at pH 4 consumed 4.04 electrons per molecule. Changes in the voltammograms that occurred during coulometry are shown in Fig. 3. Voltammogram A was performed before electrolysis was started at +0.6 v *versus* the saturated calomel electrode. After about three electrons per molecule were passed (*n* = 3.20), voltammogram B was taken; C was taken when *n* = 4.02. The UV–visible spectra and voltammetry of the electrolysis product were identical to those of oxidized II at all pH's, with UV–visible peaks at 262 and 508 nm. Reduction of the electrolysis product at −0.2 v *versus* the saturated calomel electrode consumed between 1.7 and 1.9 electrons per molecule of original I.

The voltammetric oxidation of chlorpromazine itself was studied briefly for comparison. Figure 4A is a voltammogram of chlorpromazine hydrochloride in pH 6 McIlvaine buffer at a scan rate of 0.1 v/sec. The oxidation potential was pH independent, with a value for the half-peak potential of +0.65 v *versus* the saturated calomel electrode. The absence of a reverse (reduction) wave indicates that the product of the oxidation was unstable under these conditions. At the fast scan rate of 10 v/sec (Fig. 4B), a reverse wave was apparent, indicating that the oxidized material had not had time to react to an electroinactive material. The nature and kinetics of the reactions of the oxidized form are presently under study, but an estimate of the half-life of the oxidized material from these data is 10 msec.

Table I summarizes the electrochemical data for the three compounds studied. All potentials are referred to the saturated calomel electrode; to determine the potential referred to the normal hydrogen electrode, 0.246 v must be added.



Scheme III

Table I—Half-Peak and Midpoint Potentials for Chlorpromazine Derivatives

Compound	pH 6	pH 7	pH 7.4	pH 8	Method[a]
Chlorpromazine	—	0.63	0.64	—	A
I	0.322	0.242	0.210	0.181	A
II	−0.002	−0.060	−0.080	−0.105	A
II	0.010	−0.051	−0.074	−0.103	B
6-Hydroxy derivative of dopamine[b]	−0.078	−0.160	—	−0.240	B

[a] A = potential when the current equals half the peak current for the anodic (oxidation) wave, and B = $E^{o'}$ for potentiometric titration (potential at half-titration point). [b] Data from Ref. 21.

DISCUSSION

The results of potentiometric titrations, coulometry, and voltammetry indicate that the oxidation of II is an uncomplicated two-electron process, with an accompanying loss of two hydrogen ions [Scheme I, R = $(CH_2)_3N^+H(CH_3)_2$]. Although the product of the oxidation is shown here as an *ortho*-quinone, it has been pointed out that it has some zwitterionic character due to the quinone–imine resonance form (15) (Scheme II).

For an ideal, reversible, voltammogram, the formal redox potential, $E^{o'}$, for the system is the potential when the current equals 85% of the peak current (16). Since all studied systems yielded quasireversible waves, $E^{o'}$ cannot be determined accurately from the waves. The half-peak potential, $E_{p/2}$, is a useful indication of the ease of oxidation and can be used for observations of trends and for purposes of comparison. In the case of II, it can be seen that $E_{p/2}$ and $E^{o'}$ are equal to within 10 mv.

The $E_{p/2}$ *versus* pH profile for I is nonlinear, probably due to the complex nature of the followup reactions occurring immediately after oxidation. These reactions distort the voltammetric wave, and the pH dependence is unpredictable. Due to the instability of oxidized I, potentiometric titrations were not attempted. However, for reasons discussed already, $E_{p/2}$ is a good approximation for the redox potential. The observations are consistent with the oxidation mechanism shown in Scheme III.

This mechanism is supported by the following evidence. The complete oxidation of I liberates four electrons per molecule of starting material. The product is voltammetrically and spectroscopically indistinguishable from oxidized II quinone (VI). An intermediate is observed during oxidation, which is not present after four electrons have been passed, and which has a voltammogram consistent with Structure V. The electrolysis of I occurs in two distinct phases: a rapid, initial oxidation corresponding to the consumption of I to form V and VI and a slower phase corresponding to the cyclization of V back to III and eventual complete generation of VI. The oxidation slows down when approximately three electrons have been passed per molecule of I. The reduction of the final oxidation product required 1.7–1.9 electrons per molecule. Although the suggested mechanism predicts a value of 2.0 electrons, slow degradation of the quinone might account for the low values.

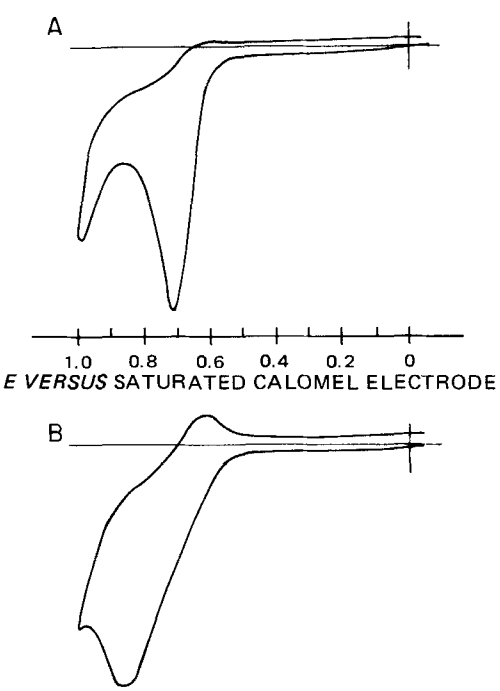


Figure 4—*Voltammograms of chlorpromazine in pH 6 McIlvaine buffer (carbon paste electrode). Key: A, scan rate = 0.1 v/sec; and B, scan rate = 10 v/sec.*

$$IV \longrightarrow IV^+ + e^-$$
$$\downarrow$$
$$IV^{2+} + e^-$$

Scheme IV

Although several reports have been published on the electrochemical oxidation of chlorpromazine in acidic media (17–19), the author is unaware of any studies near physiological pH. Figure 4 indicates that the product of the oxidation rapidly degrades to an electroinactive product, probably the sulfoxide. At a fast scan rate, the reduction of the initial product can be observed, since the product has insufficient time to degrade completely. The distortion of the oxidation wave could be caused by two distinct phenomena: adsorption of the chlorpromazine (IV) on the electrode or splitting of the wave into two one-electron oxidations (Scheme IV). Two waves are not observed at slow scan rates, since the dication rapidly degrades to the sulfoxide, shifting the disproportionation equilibrium toward the dication and resulting in a single peak at the potential of the first oxidation. Further studies are being carried out to clarify this process.

The important conclusions that can be drawn from these results are the mechanism of oxidation of I and the relative oxidation potentials of the three chlorpromazine derivatives studied. Of the molecules studied, II oxidizes at the lowest potential, near that of the 6-hydroxy derivative of dopamine (Fig. 2). The 6-amino derivative of dopamine, another cytotoxic agent, has an oxidation potential of −0.135 v *versus* the saturated calomel electrode at pH 7.4 (20), which is even closer to the dihydroxy derivative. The importance of oxidation to cytotoxic action remains unconfirmed, but the similarity of II to the catecholamine derivatives is obvious in this respect.

Although I is more difficult to oxidize, its immediate oxidation product (III) is unstable near physiological pH. Compound III can hydrolyze to the quinone (V) or hydroxylate to II and eventually oxidize to II quinone (VI). The hydrolysis of III to form V is reversible in these experiments, but interactions of V with tissue components must be considered when examining I pharmacology. Since both degradative reactions of III are fast, even slow oxidation of I would result in formation of both V and VI. The pH dependence of these reactions and the interactions of the products with tissue components are subjects of current study.

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GI Drug Absorption in Rats Exposed to Cobalt-60 γ-Radiation I: Extent of Absorption

MICHAEL E. BRADY * and WILLIAM L. HAYTON ˣ

Abstract □ The extent of absorption of sulfanilamide, bretylium tosylate, sulfisoxazole acetyl, and riboflavin was determined in rats exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated. The drugs were administered orally at 1 or 5 days postirradiation, and the amount of drug excreted in the urine was used as the measure of absorption. Following intravenous drug administration, there was no difference between irradiated and control animals in the amount of drug excreted in the urine. At 1 day postirradiation, the absorption of sulfanilamide and bretylium was not affected by radiation; the absorption of sulfisoxazole acetyl and riboflavin was increased. The fraction of sulfanilamide excreted in the urine as N^4-conjugate was increased at 1 day postirradiation. At 5 days postirradiation, there was no detectable difference between irradiated and control animals in the extent of drug absorption. The effects of radiation on the extent of absorption of orally administered drugs were most pronounced immediately following irradiation. Irradiation apparently does not affect the absorption of drugs that are normally well absorbed or poorly absorbed due to slow transport across the GI mucosa. Following irradiation, there may be an increase in the extent of absorption of drugs that are poorly absorbed due to low aqueous solubility or that are absorbed by a saturable transport mechanism.

Keyphrases □ Absorption, GI—various drugs, effect of cobalt-60 γ-radiation, rats □ Radiation, gamma—effect on GI absorption of various drugs, rats □ Sulfanilamide—GI absorption, effect of cobalt-60 γ-radiation, rats □ Bretylium tosylate—GI absorption, effect of cobalt-60 γ-radiation, rats □ Sulfisoxazole acetyl—GI absorption, effect of cobalt-60 γ-radiation, rats □ Riboflavin—GI absorption, effect of cobalt-60 γ-radiation, rats

Patients exposed to ionizing radiation for the treatment of cancer commonly receive drugs during or following radiation therapy. When the GI tract is involved in radiation therapy, its structure and function may be altered for several days. Such alterations may affect the bioavailability of orally administered drugs.

The potential mechanisms by which radiation may alter drug absorption were explored by studying the absorption of several drugs in rats that were exposed to cobalt-60 γ-radiation. The drugs used were chosen so that the absorption rate of each drug was controlled by a different step in the overall process of absorption (Table I). Experiments were performed to assess the effects of radiation on the rate and extent of absorption of each drug and on the permeability of the intestinal mucosa. The studies on the extent of drug absorption are presented here; the other studies are reported elsewhere (1, 2).

BACKGROUND

Following oral administration, the rate and extent of absorption of many drugs are determined by one or more of the following steps: dissolution in the lumen of the GI tract, transport across the GI epithelium, and gastric emptying (3, 4). The primary rate-controlling step (or steps) in the absorption of a particular drug depends on dosage formulation and on the physicochemical properties of the drug; *e.g.*, the solubility in water affects the rate of solution, and the oil/water partition coefficient affects epithelial permeability. Since drugs with low solubility in water tend to dissolve slowly following oral administration, dissolution is usually the step that controls the absorption rate of poorly water-soluble drugs. As water solubility increases, the dissolution rate increases, but the permeability of the intestinal epithelium tends to decrease due to the lipophilic nature of this barrier. The rate-controlling step in the absorption of very polar drugs is the transport of the dissolved drug across the intestinal epithelium.

The rate of gastric emptying may determine the rate of drug absorption since most drugs tend to be absorbed more rapidly from the intestine than from the stomach. For drugs that are absorbed by a saturable transport process in the intestine, slowed gastric emptying may enhance absorption by maintaining a low concentration of drug at the site of absorption for