degradation products in the capsule mixture itself. Therefore, the extraction with mobile phase removes all degradation products from the capsule matrix.

Representative samples of procarbazine hydrochloride capsules manufactured at various times were assayed for II–IV. A typical chromatogram is shown in Fig. 1B; the values for the percent degradation product found, based on the initial amount of procarbazine being 50 mg/capsule, are given in Table III. These values are all significantly below 0.5% degradation and confirm that II and III are the main degradation products while IV is only seen in a trace amount.

In previous accelerated degradation studies, II and III were found at about the 1% level after 1 month at 55°[10]. Only a very small amount of IV was found at this temperature. Sample A (Table III) had a smaller amount of III and a larger amount of IV than any other sample. This result could, in part, be due to the oxidation of III to IV as described previously (2). Another potential degradation product, *N*-isopropyltoluamide, having a retention volume of 32 ml, was not found in any sample (2–5).

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In Vitro Evidence for Ipecac Inactivation by Activated Charcoal

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Received February 9, 1977, from the *Chemical Engineering Department, Clarkson College of Technology, Potsdam, NY 13676.* Accepted for publication June 15, 1977.

Abstract □ The *in vitro* adsorption of the alkaloid emetine, a primary constituent of ipecac, on activated charcoal was studied. The results support the supposition that syrup of ipecac should not be given to counteract poisonings if activated charcoal is also to be administered.

Keyphrases □ Emetine—*in vitro* adsorption on activated charcoal □ Ipecac—*in vitro* adsorption of constituent emetine on activated charcoal □ Adsorption, *in vitro*—emetine on activated charcoal □ Charcoal, activated—*in vitro* adsorption of emetine □ Alkaloids—emetine, *in vitro* adsorption on activated charcoal

Statements occasionally appear in the literature indicating that syrup of ipecac and activated charcoal should not be given together to counteract poisonings. The reasoning is the hypothesis that the alkaloids emetine and cephaeline, which constitute more than 90% of the alkaloids of ipecac, would adsorb to the charcoal and thereby fail to act as desired, but no proof has yet been presented.

The only reference to ipecac adsorption to activated charcoal appears to be that in an 1846 paper by Garrod, which was quoted by Holt and Holz (1). Studies (2–5) on other alkaloids such as strychnine, nicotine, atropine, morphine, yohimbine, veratrine, and aconitine have clearly established a substantial affinity between alkaloids and activated charcoal. However, the extent of binding varies widely, not only with the alkaloid involved but with pH. Since alkaloids are basic, the extent of adsorption is often much less at pH values corresponding to gastric conditions than it is at a neutral pH. This result is due to the well-recognized fact (2) that ionized forms of solutes usually bind much less strongly than their nonionized forms.

In light of the lack of any data concerning the adsorption of alkaloids of ipecac on charcoal, a study of emetine adsorption was performed. Only emetine was studied since it comprises more than half of the total alkaloid content of ipecac (6). Moreover, cephaeline ($C_{28}H_{38}N_2O_4$) differs from emetine ($C_{29}H_{40}N_2O_4$) only by the lack of one methyl group, so it would be expected to behave similarly to emetine in terms of adsorption.

EXPERIMENTAL

Simulated gastric fluid USP (pepsin omitted), pH 1.2, was used for all solutions. Emetine hydrochloride[1] was dissolved to the extent of either 0.2 or 0.4 g/liter in the gastric fluid. Powdered activated charcoal[2] was washed twice with 6 *N* HCl and six times with distilled water and then was dried at 120° for 24 hr.

Various amounts of the charcoal were mixed with 10-ml aliquots of the emetine solutions in capped glass vials and shaken for 6 hr or longer. After most of the charcoal settled, the supernate was filtered through 0.45-μm pore-size microporous membranes[3]. The clear filtrate was analyzed by UV spectrophotometry at 253.6 nm. Samples of emetine solutions of known concentrations, prepared by dilution with the gastric fluid, were treated in the same manner, except that charcoal was omitted.

RESULTS

Figure 1 shows the adsorption isotherm obtained, as represented by a plot of Q^* (grams of emetine adsorbed per gram of charcoal) *versus* C_f (concentration of emetine in grams per liter in the surrounding fluid at equilibrium). The data could be fit well (by eye) with the Freundlich equation $Q^* = 0.249C_f^{0.182}$ in the range from $0 < C_f < 0.03$ and by another Freundlich expression, $Q^* = 0.177C_f^{0.0793}$, in the range of about $0.06 < C_f < 0.400$.

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Norit A, American Norit Co., Jacksonville, Fla.
[3] Amicon Corp., Lexington, Mass.

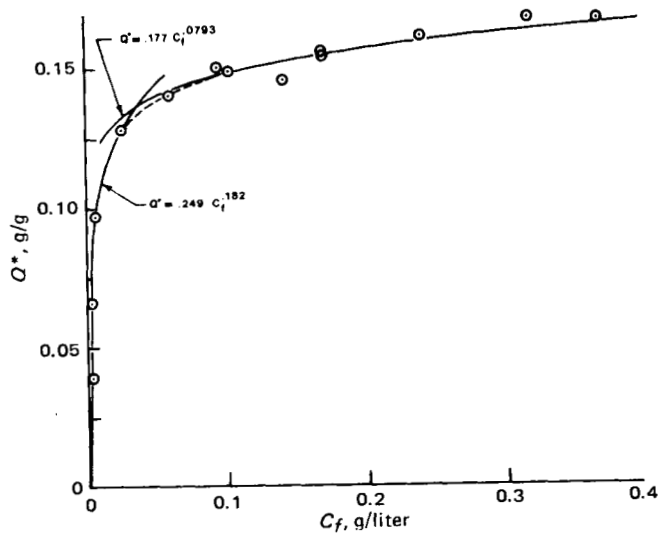

Figure 1—*Adsorption of emetine by powdered activated charcoal from simulated gastric fluid.*

DISCUSSION

On the basis that the usual dose of syrup of ipecac is 1 tablespoonful, or 15 ml (7), and that ipecac syrup yields 123–157 mg of ether-soluble alkaloids/100 ml of syrup (7), an average dose of ipecac syrup would contain about 21 mg of alkaloids. If this dose mixes with V liters of gastric contents upon ingestion, it would produce a concentration, C_0, equal to $0.021/V$ g/liter of alkaloids in the gastric contents. If one were then to administer W g of activated charcoal, adsorption of some of the alkaloids would occur, lowering their concentration to a value of C_f at equilibrium.

One can show by a simple mass balance that $Q^* = V(C_0 - C_f)/W$. If it is assumed that C_f will be lower than 0.03 g/liter (as will nearly always be the case) and if it is assumed that all alkaloids present behave like emetine in terms of adsorption, then $Q^* = 0.249C_f^{0.182}$ will pertain. Therefore, $0.249C_f^{0.182} = V(0.021/V - C_f)/W = (0.021 - VC_f)/W$. Now, it can be shown that for *any* reasonable choices of V and W, C_f will be very small. As one example, for $V = 0.5$ liter and $W = 1$ g, $C_f = 1.25 \times 10^{-6}$ g/liter, or 0.003% of the initial concentration.

This result indicates that the extent of emetine binding by any reasonable dose of activated charcoal is extremely high *in vitro*. Although *in vivo* data on emetine binding are lacking, the present results strongly suggest that there may be no acceptable dose level for syrup of ipecac that would leave enough free alkaloids in solution, after an adsorption equilibrium is attained, to cause emesis. Moreover, since the quantity of charcoal that *should* be administered to counteract poisonings effectively is as high as 120 g (8), even an extremely large dose of ipecac syrup might be inactivated under *in vivo* circumstances.

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Determination of Desmethyldiazepam in Plasma by Electron-Capture GLC: Application to Pharmacokinetic Studies of Clorazepate

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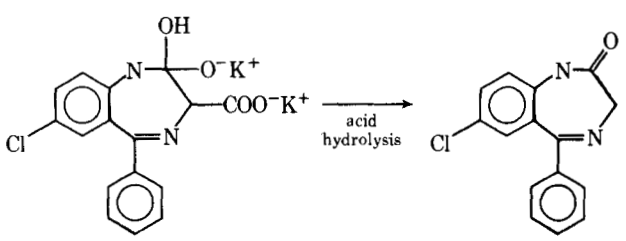
Received May 20, 1977, from the *Clinical Pharmacology Unit, Massachusetts General Hospital, Boston, MA 02114.* Accepted for publication July 18, 1977.

Abstract □ Plasma desmethyldiazepam concentrations were quantitated by a rapid and sensitive technique using electron-capture GLC. Following addition of diazepam as the internal standard, plasma is extracted at physiological pH into benzene–isoamyl alcohol. The extract is evaporated to dryness and reconstituted with toluene–isoamyl alcohol prior to chromatography. Both diazepam and desmethyldiazepam are quantitatively extracted. The variation of identical samples is 5%, and the sensitivity is 5 ng of desmethyldiazepam/ml of original sample. The method is applicable to pharmacokinetic studies of clorazepate, a benzodiazepine derivative transformed to desmethyldiazepam prior to absorption.

Keyphrases □ Desmethyldiazepam—electron-capture GLC analysis in plasma □ GLC, electron capture—analysis, desmethyldiazepam in plasma □ Clorazepate—pharmacokinetic study by GLC analysis of desmethyldiazepam in plasma □ Tranquilizers—clorazepate, pharmacokinetic study by GLC analysis of desmethyldiazepam in plasma

Clorazepate dipotassium (I) is a 1,4-benzodiazepine derivative extensively used as a sedative and antianxiety agent (1, 2). Previous studies (3) suggested that clorazepate is transformed to desmethyldiazepam (II) by hydrolysis and decarboxylation in the acidic stomach contents (Scheme I). Desmethyldiazepam is subsequently absorbed from the proximal small bowel and appears to account for most or all of the clinical effects attributable to clorazepate.



I *Scheme I* II